Washington State Health Care Authority

Health Technology Assessment

Fecal Microbiota Transplantation

Draft Evidence Report

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Fecal Microbiota Transplantation

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Abbreviations

AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
BCBS	Blue Cross Blue Shield
BMI	body mass index
C. difficile	*Clostridium difficile*
CD	Crohn's Disease
CDAD	*Clostridium difficile* associated disease
CDAI	Crohn's Disease Activity Index
CDI	*Clostridium difficile* infection
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services
CMV	Cytomegalovirus
CRP	C-reactive protein
CUA	cost utility analyses
F/U	follow-up
FDA	Food and Drug Administration
FMT	Fecal microbiota transplantation
GRADE	Grades of Recommendation Assessment, Development, and Evaluation
HBI	Harvey-Bradshaw Index
HTA	Health Technology Assessment
HTE	heterogeneity of treatment effect
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBS	irritable bowel syndrome
ICD	International classification of diseases
IND	investigational new drug
IQR	interquartile range
ISI	Institute for Scientific Information
KQ	Key Wuestion
MCID	minimum clinically important difference
MD	mean difference
mos.	months
NA	not applicable
NC	not calculable
NG	nasogastric
NGC	National Guideline Clearinghouse
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reported
NSAID	Nonsteroidal anti-inflammatory drug

PICO	patients, intervention, comparator, outcome
PUCAI	Pediatric Ulcerative Colitis Activity Index
QALY	quality-adjusted life years
QHES	Quality of Health Economic Studies
RCT	Randomized controlled trial
RD	risk difference
SCCAI	Simple Clinical Colitis Activity Index
SD	standard deviation
SoE	strength of evidence
SR	Systematic Review
SRI	Spectrum Research, Inc.
TNF	tumor necrosis factor
UC	Ulcerative Colitis

Executive Summary

Introduction

Fecal microbiota transplantation (FMT) is a procedure whereby donor fecal matter is placed into a patient's gastrointestinal system in order to recolonize it with normal gut bacteria that have been killed or suppressed. The most common use for FMT is treatment of *Clostridium difficile* infections.

Clostridium difficile infections have become increasingly common in the US in recent years. The number of diagnoses doubled between the years 2001 and 2005,[4] and it is currently estimated that *C. difficile* infects nearly 500,000 people and causes 15,000 deaths every year in the US, 80% of which occur in persons aged 65 years and older.[9,10] At the same time, infections have become more severe and difficult to treat, and the FDA currently recognizes *C. difficile* infections as one of the highest drug-resistant threats in the US.[9] The condition typically impacts older persons, particularly those who are hospitalized or in nursing home facilities, although younger persons are also at risk. The bacteria spread via fecal-to-mouth transmission, and infections most commonly impact patients who have received recent treatment with antibiotics (which disrupts the normal gut flora) and were exposed to the bacteria.[4] Other risk factors include hospitalization, older age, proton pump inhibitor use, immunosuppression, and chronic kidney disease.[4,6] Upon colonization of *C. difficile* in the colon, toxin is produced and leads to inflammation.[4] Symptoms include severe diarrhea, fever, and abdominal pain; if inadequately treated, dehydration, kidney failure, and death may result.[4,10] The infection is typically treated with the antibiotics metronidazole, vancomycin, or fidaxomicin, with metronidazole and vancomycin being first-line antibiotics, vancomycin used for more severe illness, and fidaxomicin typically reserved for recurrent infection.[4] However, approximately 20% to 60% of patients have recurrence after antibiotic treatment,[6,10,14] and those who develop multiple recurrences become increasingly resistant to antibiotic treatment.[4]

Fecal microbiota transplantation (FMT) is a treatment alternative for *C. difficile infections*, particularly those that are recurrent or resistant to standard antibiotic therapy.[4,6] Although this treatment has been used for centuries, it has only recently to gained traction in the medical community.[6] Infusion of feces from a healthy donor into the gastrointestinal tract of the infected person is thought to restore normal gut flora, which will aid in elimination of *C. difficile*.[4,6] Prior to infusion, the donor feces is screened for transmissible diseases (e.g., HIV, hepatitis, etc.).[3] Transplantation can be performed via nasogastric tube, colonoscopy, or enema; and fecal material may be either fresh or frozen.[3,5,24,38] It has been suggested that FMT is an effective treatment for *C. difficile* infections, and that the majority of patients recover after only one procedure.[3,5,6] Other conditions for which FMT use is being explored are varied, and include inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (CD).[5] However, while current FDA regulations permit use of FMT for treating *C. difficile* infections that have not

responded to standard antibiotic therapy, use of FMT for any other indication requires submittal and approval of an IND (investigational new drug) application to the FDA.[1,36]

Policy Context

Primary use is to treat individuals with difficult to treat infections caused by Clostridium difficile (*C. difficile*). Frozen stool from healthy donors is transplanted to the infected individual's bowel to restore the normal balance of bacteria in the gut. Concerns are considered medium for safety, high for efficacy, and low for cost-effectiveness.

Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of FMT for treating *C. difficile* infections or inflammatory bowel disease (IBD). The differential effectiveness and safety of FMT for subpopulations will be evaluated, as will the cost effectiveness.

Key Questions

Inclusion and exclusion criteria are summarized as follows:

Population: Patients undergoing therapeutic treatment for *Clostridium difficile* infection or inflammatory bowel disease (including ulcerative colitis and Crohn's disease)
Intervention: Fecal microbiota transplantation (FMT)

Comparators: Alternative treatment(s) (e.g., antibiotics, disease-specific medication, bowel lavage), different types of fecal preparations (e.g., fresh versus frozen), different routes of administration (e.g., nasoduodenal vs. colonoscopic)
Outcomes: Cure (CDI) (primary), death from CDI (primary), repeat or additional FMT procedures (primary), all-cause mortality (primary), disease remission/clinical improvement in disease severity (IBD) (primary), symptoms, recurrence, hospitalization, medication use, quality of life, patient satisfaction, adverse events (primary). Excluded from the scope: non-clinical and intermediate outcomes (e.g., gut microflora characteristics, biomarkers of disease).

Study design: Eligible studies compared FMT with an included comparator treatment utilizing a randomized or cohort study design. In the absence of sufficient comparative studies, case series of at least 30 patients (or 10 patients for case series of pediatric patients) were considered to provide context on the primary outcomes. For Key Question 3, case series specifically designed to evaluate harms/adverse events were considered. Only RCTs that stratified results by patient characteristics of interest so that statistical interaction (effect modification) could be evaluated were considered for Key Question 4; subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. For Key question 5, formal economic analyses were eligible for inclusion (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies).

Methods

The scope of this report and final key questions were refined based on input from clinical experts from a variety of disciplines and public comments received on draft key questions. Clinical expert input was sought to confirm critical outcomes on which to focus.

A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed to identify relevant peer reviewed literature as well as other sources (National Guideline Clearinghouse, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments.

Studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature.

Pertinent studies were critically appraised independently by two reviewers based on Spectrum's Class of Evidence (CoE) system which evaluates the methodological quality and potential for bias based on study design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results

Number of studies retained

For Key Questions 1, 2, and 3, six randomized trials, five cohort studies, and 15 case series were included. The comparisons evaluated and their respective studies are listed below; comparisons of interest not listed in the table below had no comparative evidence available that met the inclusion criteria. In addition, five economic evaluations were included, all of which evaluated the comparative impact of FMT in CDI patients.

Number of studies included for each comparison.

Comparisons	Studies
***C. difficile* Infection (CDI)**	
FMT vs. antibiotics	2 RCTs[8,11,30,31,37,38], 1 prospective cohort study[21]
Colonoscopic vs. Nasogastric FMT	1 RCT[42]
FMT after 2 vs. ≤3 CDI recurrences	1 retrospective database study[41]
FMT using frozen vs. fresh feces	1 RCT[24], 1 retrospective cohort study[35]
FMT (noncomparative)	13 case series[2,7,13,15-17,19,23,25,28,29,33,34]
Inflammatory Bowel Disease (IBD)	
FMT vs. placebo infusion	2 RCTs[27,32]
FMT (noncomparative)	1 case series[12,20]

CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease

The following provides brief summaries for comparative data on the primary outcomes of interest. Additional details are available in the Strength of Evidence Tables.

KQ1 Summary of Results

CDI: For patients with recurrent CDI, there was low quality evidence for the following outcomes as evaluated through 2.5 months. Cure was achieved by 45% (95% CI 25% to 64%) more patients following a single FMT (+ bowel lavage) procedure compared with vancomycin (± bowel lavage) therapy. Moreover, FMT procedure(s) for treatment of recurrent CDI (after the initial allocated treatment) were performed in significantly fewer patients in the FMT group than in the vancomycin group. The incidence of CDI-related as well as all-cause mortality were similar across both groups. One trial additionally provided low quality evidence of no difference between groups in all-cause mortality through eight months.

IBD: For patients with UC, moderate quality evidence suggests that clinical remission with an endoscopic response was slightly more common with FMT versus placebo through 1.75 months, however, both trials were terminated early due to lower remission rates than anticipated. No difference was found between groups in the percentage of patients who achieved clinical response through 1.75 months (low quality evidence) or in clinical remission through three months (moderate quality evidence); the need for additional procedures was also similar between groups through three months (low quality evidence). All-cause mortality was not reported. See the footnotes in the corresponding Strength of Evidence Summary table for definitions of clinical remission, clinical response, and endoscopic response.

KQ2 Summary of Results

CDI: For the comparison of frozen versus fresh feces for FMT, there was low quality evidence of no differences between groups in cure following a single procedure, mortality attributed to CDI, or all-cause mortality; all outcomes were assessed through 3.25 months. For comparisons of FMT administration route (colonoscopic versus nasogastric) as well as timing of FMT administration (early versus delayed), the quality of evidence was insufficient, thus no firm conclusions can be drawn.

IBD: No evidence.

KQ3 Summary of Results

CDI: For FMT (+ bowel lavage) versus vancomycin (± bowel lavage), there was low quality evidence of no serious adverse events through 2.5 months. Non-serious adverse events occurred similarly between groups during this same time period (low quality evidence); those reported included constipation, infection, gastrointestinal complaints, indigestion, and nausea.

For FMT using frozen versus fresh feces, no serious adverse events were reported through 12 months; non-serious adverse events occurring in the first 24 hours of FMT were reported to be similar between groups and included diarrhea, abdominal cramps, and nausea. All evidence was of low quality.

For comparisons of FMT administration route (colonoscopic versus nasogastric) as well as timing of FMT administration (early versus delayed), the quality of evidence was insufficient to draw no firm conclusions can be drawn.

IBD: For FMT versus placebo, serious adverse events (including but not limited to worsening colitis requiring colectomy, new CD diagnosis, new CDI, severe cytomegalovirus (CMV) infection) together occurred similarly between groups through three months (low quality evidence), although it was not clear whether any were treatment-related. Overall, the incidence of periprocedural non-serious adverse events were similar between groups, though increased stool frequency/diarrhea were more common with FMT while abdominal cramps occurred less frequently with FMT versus placebo.

KQ4 Summary of Results

CDI: One RCT provided data. None of the subgroups analyzed appeared to modify this outcome based on overlap of the 95% confidence intervals, including age, hospitalization status at time of FMT, strain of CDI, or CDI severity. Insufficient quality evidence precludes firm conclusions.

IBD: No evidence.

KQ5 Summary of Results

CDI: Five cost utility analyses (CUA) evaluated the impact of FMT compared with antibiotic(s) in hypothetical patients with CDI. The studies were conducted between 2011 and 2015 in the US, Canada, or Australia and the majority were conducted from a payer perspective. The time horizon varied from 90 days to one year. The clinical effectiveness outcome was reported in terms of quality-adjusted life years (QALY), the values for which were derived from published literature (e.g., RCTs, cohort studies, and/or case series). The components used to derive the QALY included cure, recurrence following initial cure, mortality, adverse events, colectomy, fulminant colitis, hospitalization, and ileostomy. In general, results from the five included CUA suggested that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI. Limitations included lack of long-term follow-up, use of hypothetical populations, use of nonrandomized studies for assumptions regarding clinical outcomes, assumed high cure rates and relatively low recurrence rates following FMT, and no analysis of severe and/or complicated CDI. Overall, the studies were relatively well-conducted.

Strength of Evidence Summaries

The following summaries of evidence have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by comparator. Details of other outcomes are available in the report.

Key Question 1 Strength of Evidence Summary: FMT vs. Vancomycin for Recurrent CDI

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
FMT + bowel lavage vs. vancomycin ± bowel lavage for recurrent CDI						
Cure* after single treatment	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N=82	Risk of bias[1] (-1) Imprecision[3] (-1)	Pooled RD 45% (95% CI 25%, 64%) Conclusion: After a single treatment, significantly more FMT patients achieved cure through 2.5 months than those in the vancomycin group.	⊕⊕◯◯ LOW
Additional FMT procedure(s)†	≤2.5 mos.	1 RCT (van Nood)	N=43	Risk of bias[1] (-1) Imprecision[3] (-1)	RD -46% (95% CI -73%, -19%) Conclusion: In 1 RCT, FMT for recurrent CDI was used in significantly fewer patients in the FMT group (24% (4/17) vs. 69% (16/26) in the vancomycin group); cure was achieved in 3/4 and 15/17 of these patients (respectively). (The other trial did not report comparative data: while 30% (6/20) of FMT patients underwent one or more additional FMTs, and 5/6 achieved cure; patients in the vancomycin group were not offered FMT.)	⊕⊕◯◯ LOW
Mortality attributed to CDI	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N=79	Risk of bias[1] (-1) Imprecision[3] (-1)	Pooled RD 0% (95% CI -9%, 8%) Conclusion: No difference between groups. One trial (Cammarota) reported 2 deaths from CDI in each group; the other trial (van Nood) reported 0 deaths in both groups.	⊕⊕◯◯ LOW
All-cause mortality	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N=79	Risk of bias[1] (-1) Imprecision[3] (-1)	Pooled RD -4% (95% CI -14%, 7%)) Conclusion: No difference between groups. One trial (Cammarota) reported 2 deaths from CDI in each group; the other trial (van Nood) reported 0 deaths in the FMT group and 1 death in the vancomycin group.	⊕⊕◯◯ LOW
	≤8 mos.	1 RCT (Cammarota)	N=36	Risk of bias[1] (-1) Imprecision[3] (-1)	RD -23% (95% CI -51%, 6%)) Conclusion: No difference between groups. There were 3 deaths in the FMT group (2 of which from CDI) and 6 in the vancomycin group (2 of which from CDI).	⊕⊕◯◯ LOW

CDI: Clostridium difficile infection; CI: Confidence interval; RD: risk difference

* Cure was defined as the absence of CDI-related diarrhea (loose or watery stools ≥3 times per day for ≥2 consecutive days, or ≥8 times within previous 2 days) plus two (Cammarota) or three (van Nood) negative stool tests for C. difficile toxin.

†In both trials, patients in the FMT group were offered repeat FMT upon relapse of CDI: feces from a different donor was used in one trial (van Nood); the other trial (Cammarota) repeated FMT every 3 days until resolution was achieved.

Recurrence of CDI following vancomycin (± bowel lavage) was handled differently between the trials: while the Cammarota trial did not treat control group patients with FMT (in fact, it was unclear what (if any) treatment was offered these patients); the van Nood trial offered FMT off-protocol to these patients following recurrence of CDI.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size

Key Question 1 Strength of Evidence Summary: FMT vs. Placebo for IBD (UC)

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
FMT* vs. placebo* for IBD (UC)						
Clinical remission + endoscopic response†	1.75 mos.	1 RCT (Moayyedi)	N=75	Imprecision[3] (-1)	RD 18% (95% CI 3%, 34%) Conclusion: While slightly more FMT than placebo* patients achieved this outcome (24% vs. 5%), the trial was ended early due to futility. A second smaller trial at moderately high risk of bias due to a number of methodological flaws (Rossen, N=48) reported a similar direction of effect, although the results did not reach statistical significance due to small sample size (30% vs. 20%, RD 10% (95% CI -14%, 35%) and was also ended early because of futility.	⊕⊕⊕◯ MODERATE
	12 mos.	1 RCT (Moayyedi)	N=38	Risk of bias[1] (-1) Imprecision[3,4] (-2)	Conclusion: This outcome was achieved by 21% (8/38) of patients in the FMT group but was not evaluated in the placebo group. No firm conclusions can be made due to insufficient quality of evidence.	⊕◯◯◯ INSUFFICIENT
Clinical remission‡	3 mos.	1 RCT (Rossen)	N=48	Risk of bias[2] (-1) Imprecision[3] (-1)	RD -2% (95% CI -28%, 25%) Conclusion: No difference between FMT and placebo* groups (30% vs. 32%).	⊕⊕◯◯ LOW
Clinical response§	1.75 mos.	1 RCT (Moayyedi)	N=75	Imprecision[3] (-1)	RD 15% (95% CI -6%, 36%) Conclusion: No difference between FMT and placebo* groups (39% vs. 24%). A second smaller trial at moderately high risk of bias due to a number of methodological flaws (Rossen, N=48) reported similar results at 3 months (48% vs. 52%, RD -4% (95% CI -32%, 24%)).	⊕⊕⊕◯ MODERATE

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
Additional procedures	3 mos.	1 RCT (Rossen)	N=48	Risk of bias[2] (-1) Imprecision[3] (-1)	RD 10% (95% CI -11%, 31%) Conclusion: No difference between FMT and placebo* groups (22% vs. 12%) in the need for rescue therapy (not defined) for ongoing disease flare.	⊕⊕◯◯ LOW
All-cause mortality	Any	0 studies			No evidence.	⊕◯◯◯ INSUFFICIENT

CI: confidence interval; F/U: follow-up;; NR: not reported; RD: risk difference

* Treatment groups:

- Moayyedi: FMT vs. water (placebo) via retention enema.
- Rossen: FMT + bowel lavage using donor feces vs. autologous feces (placebo).

† Clinical remission plus endoscopic response definitions:

- Moayyedi: full Mayo Clinic score <3 (range 0-12 (worst)) and complete healing of the mucosa during flexible sigmoidoscopy/ endoscopic Mayo Clinic score of 0
- Rossen 2015: SCCAI score ≤2 (range 0-19 (worst)) and ≥1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum (as compared with baseline sigmoidoscopy) 12 weeks after the first treatment.

‡ Defined as a SCCAI score ≤2. At 12 weeks, 0% (0/23) vs. 8% (2/25) in the FMT vs. control group were no longer in remission after being in remission at week 6 and 4% (1/23) vs. 8% (2/25), respectively, were in remission after not being in remission at week 6.

§ Clinical response definitions:

- Moayyedi: reduction in full Mayo clinic score of ≥3 points (range 0-12 (worst)).
- Rossen 2015: reduction of ≥1.5 points on the SCCAI (range 0-19 (worst)).

Reasons for downgrading:

1. Serious risk of bias: the study violated one or more of the criteria for good quality RCT related to the outcome reported: for 12 month data, patients were not blinded.
2. Serious risk of bias: the study violated one or more of the criteria for good quality RCT related to the outcome reported
3. Inconsistency: differing estimates of effects across trials
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or wide confidence interval
5. Imprecise effect estimate: unknown confidence interval (no results reported for placebo group)

Key Question 2 Strength of Evidence Summary: Comparisons of FMT Administration Routes

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
CDI: Colonoscopic FMT vs. Nasogastric (NG) FMT						
Cure* after single treatment	≤2 mos.	1 RCT (Youngster)	N=20	Risk of bias[1] (-1) Imprecision[3] (-2)	RD 20% (95% CI -19%, 59%) Conclusion: No statistical difference between colonoscopic and NG tube infusion (80% (8/10) vs. 60% (6/10)). No firm conclusions can be made due to insufficient quality of evidence.	⊕○○○ INSUFFICIENT
Additional FMT procedure(s)	≤2 mos.	1 RCT (Youngster)	N=20	Risk of bias[1] (-1) Imprecision[3] (-2)	RD -10% (95% CI -48%, 28%) Conclusion: No statistical difference between groups (20% (2/10) vs. 30% (3/10)); cure was achieved in 2/2 and 2/3 of these patients (respectively). No firm conclusions can be made due to insufficient quality of evidence.	⊕○○○ INSUFFICIENT
Mortality attributed to CDI	≤2 mos.	1 RCT (Youngster)	N=20	Risk of bias[1] (-1) Imprecision[3] (-2)	RD 0% Conclusion: No events in either group (0% vs. 0%). No firm conclusions can be made due to insufficient quality of evidence.	⊕○○○ INSUFFICIENT
All-cause mortality	≤6 mos.	1 RCT (Youngster)	N=20	Risk of bias[1] (-1) Imprecision[3] (-2)	Conclusion: Comparative data not reported. Two patients (10%) died through 6 months f/u; the treatment group was not reported. No firm conclusions can be made due to insufficient quality of evidence.	⊕○○○ INSUFFICIENT
IBD: Comparisons of FMT Administration Routes						
Any	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT

CDI: *Clostridium difficile* infection; CI: confidence interval; IBD: inflammatory bowel disease; NG: nasogastric; RD: risk difference

* Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and confidence interval includes both negligible effect and appreciable benefit or harm for treatment group

Key Question 2 Strength of Evidence Summary: Comparisons of Timing of FMT Administration

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
CDI: "Timely" vs. "Delayed" FMT (i.e., following 2 vs. ≥3 recurrences of CDI)						
Cure* after single treatment	≤3 mos.	1 retro. cohort study (Waye)	N=75	Risk of bias[1] (-1) Imprecision[3] (-1)	Conclusion: No difference between "timely" versus "delayed" FMT (i.e., FMT after 2 vs. ≥3 CDI recurrences) (94% (28/30) vs. 93% (42/45), p=0.93). No firm conclusions can be made due to insufficient quality of evidence.	⊕○○○ INSUFFICIENT
Additional FMT procedure(s)	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT
Mortality attributed to CDI	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT
All-cause mortality	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT
IBD: Comparisons of timing of FMT Administration						
Any	Any	0 studies			No evidence.	⊕○○○ INSUFFICIENT

CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease

* Cure was not clearly defined. The study did define recurrence of CDI as diarrhea (≥3 loose stools per day) plus a positive stool toxin test occurring in less than two months from the time the previous course of antibiotics was completed.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size

Key Question 2 Strength of Evidence Summary: Comparisons of Fecal Preparations

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
CDI: FMT using Frozen vs. Fresh Feces						
Cure* after single treatment	≤3.25 mos.	1 RCT (Lee)	N= 219	Risk of bias[1] (-1) Imprecision[3] (-1)	RD 2.3% (95% CI -10.9%, 15.6%) Conclusion: No difference between frozen vs. fresh feces for FMT infusion (52.8% (57/108) vs. 50.5% (56/111)).	⊕⊕◯◯ LOW
Additional FMT procedure(s)	Any	0 studies			No evidence.	⊕◯◯◯ INSUFFICIENT
Mortality attributed to CDI	≤3.25 mos.	1 RCT (Lee)	N= 219	Risk of bias[1] (-1) Imprecision[4] (-1)	RD 0.1% (95% CI -3.5%, 3.6%) Conclusion: No difference between frozen vs. fresh feces for FMT infusion (1.9% (2/108) vs. 1.8% (2/111)).	⊕⊕◯◯ LOW
All-cause mortality	≤3.25 mos.	1 RCT (Lee)	N= 219	Risk of bias[1] (-1) Imprecision[3] (-1)	RD -6.2% (95% CI -13.5%, 1.2%) Conclusion: No statistical difference between frozen vs. fresh feces for FMT infusion, although the incidence of death from any cause was slightly lower in the frozen feces group (5.6% (6/108) vs. 11.7% (13/111)).	⊕⊕◯◯ LOW
IBD: Comparisons of timing of FMT Administration						
Any	Any	0 studies			No evidence.	⊕◯◯◯ INSUFFICIENT

CDI: *Clostridium difficile* infection; CI: confidence interval; IBD: inflammatory bowel disease; RD: risk difference

* Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: confidence interval includes both negligible effect and appreciable benefit or harm for treatment group
4. Imprecise effect estimate for a dichotomous outcome: rare outcome and small sample size

Key Question 3 Strength of Evidence Summary: Safety of FMT for CDI

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
FMT + bowel lavage vs. vancomycin ± bowel lavage for recurrent CDI: FMT-related adverse events						
Serious adverse events	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N=82	Risk of bias[1] (-1) Imprecision[3] (-1)	RD 0% Conclusion: No serious adverse events (including death) occurred in either treatment group.	⊕⊕◯◯ LOW
Non-serious adverse events	≤2.5 mos.	1 RCT (van Nood)	N=43	Risk of bias[1] (-1) Imprecision[3] (-1)	Conclusion: the following non-serious adverse events occurred with statistically similar frequency between FMT and vancomycin groups as measured between the first day after treatment and 2.5 months follow-up: • Constipation (19% vs. 12%, RD 7% (95% CI -16%, 30%) • Infection (13% vs. 4%, RD 9% (95% CI -9%, 26%)) • Gastrointestinal complaints (0% vs. 8%, RD -8% (95% -18%, 3%)) • Indigestion (0% vs. 4%, RD -4% (95% CI -11%, 4%)) • Nausea (0% vs. 4%, RD -4% (95% CI -11%, 4%)) • Belching (0% vs. 0%) • Vomiting (0% vs. 0%) • Abdominal cramps or pain (0% vs. 0%) • Diarrhea (0% vs. 0%)	⊕⊕◯◯ LOW
Colonoscopic FMT vs. Nasogastric (NG) FMT for recurrent or refractory CDI: FMT-related adverse events						
Serious adverse events	≤2-6 mos.	1 RCT (Youngster)	N=20	Risk of bias[1] (-1) Imprecision[3] (-2)	RD: 0% Conclusion: No serious adverse events were attributed to FMT over 2 months of follow-up, including death which was measured through 6 months. No firm conclusions can be made due to insufficient quality of evidence.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	0 studies			No comparative evidence	⊕◯◯◯ INSUFFICIENT

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
"Timely" vs. "Delayed" FMT (i.e., following 2 vs. ≥3 recurrences of CDI): FMT-related adverse events						
Serious adverse events	Any	0 studies			No comparative evidence	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	0 studies			No comparative evidence	⊕◯◯◯ INSUFFICIENT
FMT using Frozen vs. Fresh Feces for recurrent CDI: FMT-related adverse events						
Serious adverse events	≤3.25-12 mos.	1 RCT (Lee) 1 cohort study (Satokari)	N=261	Risk of bias[1] (-1) Imprecision[3] (-1)	RD: 0% Conclusion: No serious adverse events (including death) were attributed to FMT using feces prepared by either method as reported by the RCT (N=219) and cohort study (N=42).	⊕⊕◯◯ LOW
Non-serious adverse events	≤24 hours	1 RCT (Lee)	N=232	Risk of bias[1] (-1) Imprecision[5] (-1)	Conclusion: One trial reported the following mild to moderate symptoms occurred similarly between groups, however data were not stratified by groups and patient numbers were not reported: • Transient diarrhea: 70% • Abdominal cramps: 10% • Nausea: <5%	⊕⊕◯◯ LOW
Non-serious adverse events	≤12 mos.	1 cohort study (Satokari)	N=42	Risk of bias[1] (-1) Imprecision[3] (-1)	Conclusion: No firm conclusions can be made due to insufficient quality of evidence.	⊕◯◯◯ INSUFFICIENT
Noncomparative: FMT-related adverse events (any route, preparation)						
Serious adverse events	≤2-24 mos.	1 cohort study (Lagier) 8 case series (Rubin, Kelly, Brandt, Mattila, Orenstein, Agrawal, Patel, Lee)	N=640	Risk of bias[1] (-1) Imprecision[3,5] (-2)	Conclusion: No firm conclusions can be made due to insufficient quality of evidence.	⊕◯◯◯ INSUFFICIENT‡
Non-serious adverse events	≤48 hours	3 RCTs (van Nood, Cammarota, Youngster) 1 cohort study (Lagier) 2 case series	N=146 (+ 33 FMTs)	Risk of bias[1] (-1) Imprecision[5] (-1)	Conclusion: For the studies in which no comparative data were reported, the following non-serious FMT-related adverse events were documented across 3 RCTs (N=56), 1 cohort study (33 FMTs), and 3 case series	⊕⊕◯◯ LOW§

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality

		(Kelly, Kronman)			(N=90). The following details were reported:
					• *Diarrhea: 73% - 94%*
					  • 2 RCTs: 94% (34/36 across both RCTs)
					  • 1 cohort study: 73% (24/33 FMTs)
					• *Abdominal cramps: 47%*
					  • 2 RCTs: 47% (17/36 across 2 RCTs)
					• *Abdominal discomfort/pain: 4% - 39%*
					  • 2 RCTs: 39% (14/36 across 2 RCTs)
					  • 1 case series: 4% (3/80) (with bloating)
					• *Nausea: 3% - 6%*
					  • 1 RCT: 6% (1/16)
					  • 1 cohort study: 3% (1/33 FMTs); nausea described as uncontrollable
					• *Fever: 1% - 5%*
					  • 1 RCT: 5% (1/20) (2 days post-FMT, transient)
					  • 1 case series: 1% (1/80)
					• *Belching: 19%*
					  • 1 RCT: 19% (3/19)
					• *Minor mucosal tear during colonoscopy: 1%*
					  • 1 case series: 1% (1/80)
					• *Mucoid stools: 10%*
					  • 1 case series of pediatric patients: 10% (1/10 across both studies)
					• *Vomiting: 0% - 10%*
					  • 1 RCT: 0% (0/16)
					  • 1 case series of pediatric patients: 10% (1/10)
					• *Constipation: 0%*
					  • 1 RCT: 0% (0/16)
					• *Dizziness with diarrhea: 6%*
					  • 1 RCT: 6% (1/16) (patient had autonomic dysfunction)
					• *Refusal of nasogastric tube: 3%*
					• 1 cohort study: 3% (1/33 FMTs)	

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
Non-serious adverse events	>48 hours to 2.5 mos.	2 RCTs (Youngster, Lee) 8 case series (Kelly, Agrawal, Lee, Russell, Rubin, Orenstein, Jorup-Rostrum, Garborg)	N=763	Risk of bias[1] (-1) Imprecision[5] (-1)	Conclusion: No firm conclusions can be made due to insufficient quality of evidence.	⨁◯◯◯ INSUFFICIENT‡

CDI: *Clostridium difficile* infection; NG: nasogastric; RD: risk difference

*The patient had esophageal cancer and cachexia, aspirated during sedation for the FMT procedure, and died the next day from respiratory failure.

†Microperforation occurred as a result of periprocedural biopsy in small bowel in region believed to have ischemic injury; patient recovered with conservative treatment.

‡Because the majority of the evidence is from nonrandomized studies and case series, the overall SoE started at "Low" and was then downgraded from there.

§Because the majority of the evidence is from RCTs, the overall SoE started at "High" and was then downgraded from there.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size, rare event
4. Imprecise effect estimate for a dichotomous outcome: confidence interval includes both negligible effect and appreciable benefit or harm for treatment group
5. Imprecise effect estimate for a dichotomous outcome: unknown confidence interval

Key Question 3 Strength of Evidence Summary: Safety of FMT for IBD

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
FMT vs. placebo for IBD						
Serious adverse events	1.75-3 mos.	2 RCTs (Moayyedi, Rossen)	N=123	Risk of bias[1] (-1) Imprecision[4] (-1)	Pooled RD 2% (95% CI -7%, 11%) Conclusion: Both RCTs reported no difference between groups in the overall incidence of "serious" adverse events (pooled, 8% (5/61) vs. 6% (4/62)), including: • Worsening colitis requiring colectomy: 0% (0/38) vs. 3% (1/37) (1 RCT) • New diagnosis of CD: 5% (2/38) vs. 3% (1/37) (1 RCT) • C. difficile infection: 3% (1/38) vs. 0% (0/37) (1 RCT) • Severe illness from CMV infection: 0% (0/23) vs. 4% (1/25) (1 RCT) • Severe small bowel CD, late abdominal pain, and operation for cervical carcinoma: not stratified by treatment group in one RCT Whether any of these events were directly related to FMT treatment is not clear.	⊕⊕◯◯ LOW
Non-serious adverse events	Peri-procedural	1 RCT (Rossen)	N=23	Risk of bias[1] (-1) Imprecision[4] (-1)	78% (18/23) vs. 64% (16/25), RD 14% (-11%, 40%) Conclusion: There was no difference between groups in the overall incidence of FMT-related non-serious adverse events. • Increased stool frequency/diarrhea was more common with FMT (30% vs. 4%, RD 26% (95% CI 6%, 47%)). • Abdominal cramps were less common with FMT (0% vs. 24%, RD -24% (95% CI -41%, -7%))	⊕⊕◯◯ LOW

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
					All other peri-procedural events occurred with similar frequency between groups.†	
Noncomparative: FMT-related adverse events						
Serious adverse events	0.75-15 mos.	1 RCT (Moayyedi) 1 case series (Cui)	N= 68	Risk of bias[1] (-1) Imprecision[3, 5] (-2)	Conclusion: No firm conclusions can be made due to insufficient quality of evidence.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Peri-procedural	2 case series (Cui, Kunde)	N= 40	Risk of bias[1] (-1) Imprecision[5] (-1)	Conclusion: No firm conclusions can be made due to insufficient quality of evidence.	⊕◯◯◯ INSUFFICIENT*
Non-serious adverse events	1-15 mos.	2 case series (Cui, Kunde)	N= 40	Risk of bias[1] (-1) Imprecision[5] (-1)	Conclusion: No firm conclusions can be made due to insufficient quality of evidence.	⊕◯◯◯ INSUFFICIENT*

CD: Crohn's disease; CI: confidence interval; CMV: Cytomegalovirus; IBD: Inflammatory Bowel Disease; RD: risk difference

*Because the majority of the evidence is from nonrandomized studies and case series, the overall SoE started at "Low" and was then downgraded from there.

†Other periprocedural non-serious adverse events included (in decreasing order of frequency): abdominal murmurs, abdominal pain, nausea, fever, vomiting of fecal infusion due to malposition of tube, discomfort during tube placement, headache, vomiting of bowel preparation after replacement of nasoduodenal tube before FMT start, vomiting, mild constipation, dizziness, malaise, and infectious complications.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size, rare event
4. Imprecise effect estimate for a dichotomous outcome: confidence interval includes both negligible effect and appreciable benefit or harm for treatment group.
5. Imprecise effect estimate for a dichotomous outcome: unknown confidence interval

Key Question 4 Strength of Evidence Summary: Differential Efficacy and Safety Results

Outcome	F/U	Studies	N	Reasons for Downgrading	Conclusion	Quality
CDI: Frozen vs. Fresh Feces for FMT						
Differential Efficacy or Safety	13 weeks after the last FMT	1 RCT (Lee)	N= 219	Risk of bias[1,2] (-2) Imprecision[3] (-1)	Conclusion: Insufficient evidence precludes firm conclusions. None of the subgroups analyzed appeared to modify this outcome based on overlap of the 95% confidence intervals, including age, hospitalization status at time of FMT, strain of CDI, or CDI severity.	⊕◯◯◯ INSUFFICIENT
CDI: All other comparisons						
Differential Efficacy or Safety	Any	0 RCTs			No evidence	⊕◯◯◯ INSUFFICIENT
IBD						
Differential Efficacy or Safety	Any	0 RCTs			No evidence	⊕◯◯◯ INSUFFICIENT

CDI: *Clostridium difficile* infection; IBD: Inflammatory Bowel Disease

Reasons for downgrading:

1. Serious risk of bias: the study violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Serious risk of bias in evaluation of HTE: no formal test for interaction was done; relatively high number of subgroups tested; no hypotheses stated regarding impact of subgroups on cure rate
3. Imprecise effect estimate for a dichotomous outcome: small sample size

Key Question 5 Strength of Evidence Summary: Cost Effectiveness

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. As such, a summary of the results from these studies is provided below.

CDI

Study characteristics

Five cost utility analyses (CUA)[18,22,26,39,40] were included and evaluated the impact of FMT compared with antibiotic(s) in hypothetical patients with CDI. Four[18,22,39,40] of the CUA were relatively well-conducted, with QHES scores ranging from 71 to 89; one of the studies[26] had more methodological limitations, with a QHES score of 54 (Appendix Table E4).

The studies were conducted between 2011 and 2015 in the US[18,39,40], Canada[22], or Australia[26] and the majority were conducted from a payer perspective. The time horizon varied from 90 days to one year. Costs were reported in 2011 to 2015 US, Canadian, or Australian dollars. Cost data were derived from a variety of sources, including CMS in the three studies conducted from a US perspective. The components of cost data included that of the treatment (typically to include donor testing for FMT), hospitalization for recurrent CDI, adverse events, and outpatient visits.

The clinical effectiveness outcome was reported in terms of quality-adjusted life years (QALY), the values for which were derived from published literature (e.g., RCTs, cohort studies, and/or case series). The components used to derive the QALY included cure, recurrence following initial cure, mortality, adverse events, colectomy, fulminant colitis, hospitalization, and ileostomy. In general, assumed cure rates for recurrent CDI following FMT (any route) as reported by the economic analyses were higher (range, 81.3% to 94.5%) than those reported following a single FMT (any route) as reported by studies included in this HTA (RCTs: range, 51.5% to 80%; cohort studies: range, 93% to 96%; case series: range 52% to 94%).

Results

FMT via colonoscopy was found to be dominant[40] or more cost effective[18,22,26] compared to vancomycin in all four studies of patients with recurrent CDI. Conclusions were similar when comparing FMT to metronidazole[18,22] or fidaxomicin[18,22]. For the initial CDI occurrence, one study[39] found that FMT via colonoscopy was dominant over vancomycin alone. In general, sensitivity analyses supported the conclusion that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI.

Conclusions and Limitations

In general, results from the five included CUA suggested that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI. Limitations included lack of long-term follow-up, use of hypothetical populations, use of nonrandomized studies for assumptions regarding clinical outcomes, assumed high cure rates and relatively low recurrence rates following FMT, and no analysis of severe and/or complicated CDI. Overall, the studies were relatively well-conducted.

IBD

No full economic evaluations were conducted on patients with IBD.

References

1. Administration. UFaD. Guidance for industry: Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat Clostridium difficile infection not responsive to standard therapies. Available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm361379.htm. 2013.
2. Agrawal M, Aroniadis OC, Brandt LJ, et al. The Long-term Efficacy and Safety of Fecal Microbiota Transplant for Recurrent, Severe, and Complicated Clostridium difficile Infection in 146 Elderly Individuals. J Clin Gastroenterol 2015.
3. Allegretti JR, Korzenik JR, Hamilton MJ. Fecal microbiota transplantation via colonoscopy for recurrent C. difficile Infection. J Vis Exp 2014.
4. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults: a systematic review. JAMA 2015;313:398-408.
5. Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. Curr Gastroenterol Rep 2013;15:337.
6. Bowman KA, Broussard EK, Surawicz CM. Fecal microbiota transplantation: current clinical efficacy and future prospects. Clin Exp Gastroenterol 2015;8:285-91.
7. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol 2012;107:1079-87.
8. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther 2015;41:835-43.
9. Centers for Disease Control and Prevention. Antibiotic/Antimicrobial Resistance: Biggest Threats: Clostridium Difficile. Available at: http://www.cdc.gov/drugresistance/biggest_threats.html 2015.
10. Centers for Disease Control and Prevention. Nearly half a million Americans suffered from Clostridium diccile infections in a single year: Press release. Available at: http://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html. 2015.
11. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. Br J Sports Med 2011;45:966-71.
12. Cui B, Feng Q, Wang H, et al. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. J Gastroenterol Hepatol 2015;30:51-8.
13. Garborg K, Waagsbo B, Stallemo A, Matre J, Sundoy A. Results of faecal donor instillation therapy for recurrent Clostridium difficile-associated diarrhoea. Scand J Infect Dis 2010;42:857-61.
14. Johns Hopkins Medicine. Fecal transplantation (bacteriotherapy). Available at: http://www.hopkinsmedicine.org/gastroenterology_hepatology/clinical_services/advanced_endoscopy/fecal_transplantation.html.

15. Jorup-Ronstrom C, Hakanson A, Sandell S, et al. Fecal transplant against relapsing Clostridium difficile-associated diarrhea in 32 patients. Scand J Gastroenterol 2012;47:548-52.
16. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol 2014;109:1065-71.
17. Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol 2016.
18. Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of competing strategies for management of recurrent Clostridium difficile infection: a decision analysis. Clin Infect Dis 2014;58:1507-14.
19. Kronman MP, Nielson HJ, Adler AL, et al. Fecal microbiota transplantation via nasogastric tube for recurrent clostridium difficile infection in pediatric patients. J Pediatr Gastroenterol Nutr 2015;60:23-6.
20. Kunde S, Pham A, Bonczyk S, et al. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. J Pediatr Gastroenterol Nutr 2013;56:597-601.
21. Lagier JC, Delord M, Million M, et al. Dramatic reduction in Clostridium difficile ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: a preliminary report. Eur J Clin Microbiol Infect Dis 2015;34:1597-601.
22. Lapointe-Shaw L, Tran KL, Coyte PC, et al. Cost-Effectiveness Analysis of Six Strategies to Treat Recurrent Clostridium difficile Infection. PLoS One 2016;11:e0149521.
23. Lee CH, Belanger JE, Kassam Z, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. Eur J Clin Microbiol Infect Dis 2014;33:1425-8.
24. Lee CH, Steiner T, Petrof EO, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 2016;315:142-9.
25. Mattila E, Uusitalo-Seppala R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology 2012;142:490-6.
26. Merlo G, Graves N, Brain D, Connelly L. Economic Evaluation of Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile Infection in Australia. J Gastroenterol Hepatol 2016.
27. Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology 2015;149:102-9 e6.
28. Orenstein R, Dubberke E, Hardi R, et al. Safety and Durability of RBX2660 (Microbiota Suspension) for Recurrent Clostridium difficile Infection: Results of the PUNCH CD Study. Clin Infect Dis 2015.
29. Patel NC, Griesbach CL, DiBaise JK, Orenstein R. Fecal microbiota transplant for recurrent Clostridium difficile infection: Mayo Clinic in Arizona experience. Mayo Clin Proc 2013;88:799-805.
30. Raeissadat SA, Rayegani SM, Hassanabadi H, Rahimi R, Sedighipour L, Rostami K. Is Platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: one year randomized clinical trial. BMC Sports Sci Med Rehabil 2014;6:12.

31. Raeissadat SA, Sedighipour L, Rayegani SM, Bahrami MH, Bayat M, Rahimi R. Effect of Platelet-Rich Plasma (PRP) versus Autologous Whole Blood on Pain and Function Improvement in Tennis Elbow: A Randomized Clinical Trial. Pain Res Treat 2014;2014:191525.
32. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 2015;149:110-8 e4.
33. Rubin TA, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. Anaerobe 2013;19:22-6.
34. Russell GH, Kaplan JL, Youngster I, et al. Fecal transplant for recurrent Clostridium difficile infection in children with and without inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2014;58:588-92.
35. Satokari R, Mattila E, Kainulainen V, Arkkila PE. Simple faecal preparation and efficacy of frozen inoculum in faecal microbiota transplantation for recurrent Clostridium difficile infection--an observational cohort study. Aliment Pharmacol Ther 2015;41:46-53.
36. Smith MB, Kelly C, Alm EJ. Policy: How to regulate faecal transplants. Nature 2014;506:290-1.
37. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. Am J Sports Med 2011;39:2130-4.
38. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013;368:407-15.
39. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of treatment strategies for initial Clostridium difficile infection. Clin Microbiol Infect 2014;20:1343-51.
40. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of fecal microbiota transplantation for recurrent Clostridium difficile infection. Infect Control Hosp Epidemiol 2015;36:438-44.
41. Waye A, Atkins K, Kao D. Cost Averted With Timely Fecal Microbiota Transplantation in the Management of Recurrent Clostridium difficile Infection in Alberta, Canada. J Clin Gastroenterol 2016.
42. Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis 2014;58:1515-22.

1. Appraisal

1.1 Background and Rationale

Fecal microbiota transplantation (FMT) is a procedure whereby donor fecal matter is placed into a patient's gastrointestinal system in order to recolonize it with normal gut bacteria that have been killed or suppressed. The most common use for FMT is treatment of *Clostridium difficile* infections.

Clostridium difficile infections have become increasingly common in the US in recent years. The number of diagnoses doubled between the years 2001 and 2005,[10] and it is currently estimated that *C. difficile* infects nearly 500,000 people and causes 15,000 deaths every year in the US, 80% of which occur in persons aged 65 years and older.[26,27] At the same time, infections have become more severe and difficult to treat, and the FDA currently recognizes *C. difficile* infections as one of the highest drug-resistant threats in the US.[26] The condition typically impacts older persons, particularly those who are hospitalized or in nursing home facilities, although younger persons are also at risk. The bacteria spread via fecal-to-mouth transmission, and infections most commonly impact patients who have received recent treatment with antibiotics (which disrupts the normal gut flora) and were exposed to the bacteria.[10] Other risk factors include hospitalization, older age, proton pump inhibitor use, immunosuppression, and chronic kidney disease.[10,18] Upon colonization of *C. difficile* in the colon, toxin is produced and leads to inflammation.[10] Symptoms include severe diarrhea, fever, and abdominal pain; if inadequately treated, dehydration, kidney failure, and death may result.[10,27] The infection is typically treated with the antibiotics metronidazole, vancomycin, or fidaxomicin, with metronidazole and vancomycin being first-line antibiotics, vancomycin used for more severe illness, and fidaxomicin typically reserved for recurrent infection.[10] However, approximately 20% to 60% of patients have recurrence after antibiotic treatment,[18,27,62] and those who develop multiple recurrences become increasingly resistant to antibiotic treatment.[10]

Fecal microbiota transplantation (FMT) is a treatment alternative for *C. difficile infections*, particularly those that are recurrent or resistant to standard antibiotic therapy.[10,18] Although this treatment has been used for centuries, it has only recently to gained traction in the medical community.[18] Infusion of feces from a healthy donor into the gastrointestinal tract of the infected person is thought to restore normal gut flora, which will aid in elimination of *C. difficile*.[10,18] Prior to infusion, the donor feces is screened for transmissible diseases (e.g., HIV, hepatitis, etc.).[5] Transplantation can be performed via nasogastric tube, colonoscopy, or enema; and fecal material may be either fresh or frozen.[5,17,78,131] It has been suggested that FMT is an effective treatment for *C. difficile* infections, and that the majority of patients recover after only one procedure.[5,17,18] Other conditions for which FMT use is being explored are varied, and include inflammatory bowel disease, ulcerative colitis, and Crohn's disease.[17] However, while current FDA regulations permit use of FMT for treating *C. difficile* infections that have not

responded to standard antibiotic therapy, use of FMT for any other indication requires submittal and approval of an IND (investigational new drug) application to the FDA.[3,122]

Policy Context

Primary use is to treat individuals with difficult to treat infections caused by Clostridium difficile (*C. difficile*). Frozen stool from healthy donors is transplanted to the infected individual's bowel to restore the normal balance of bacteria in the gut. Concerns are considered medium for safety, high for efficacy, and low for cost-effectiveness.

Objectives

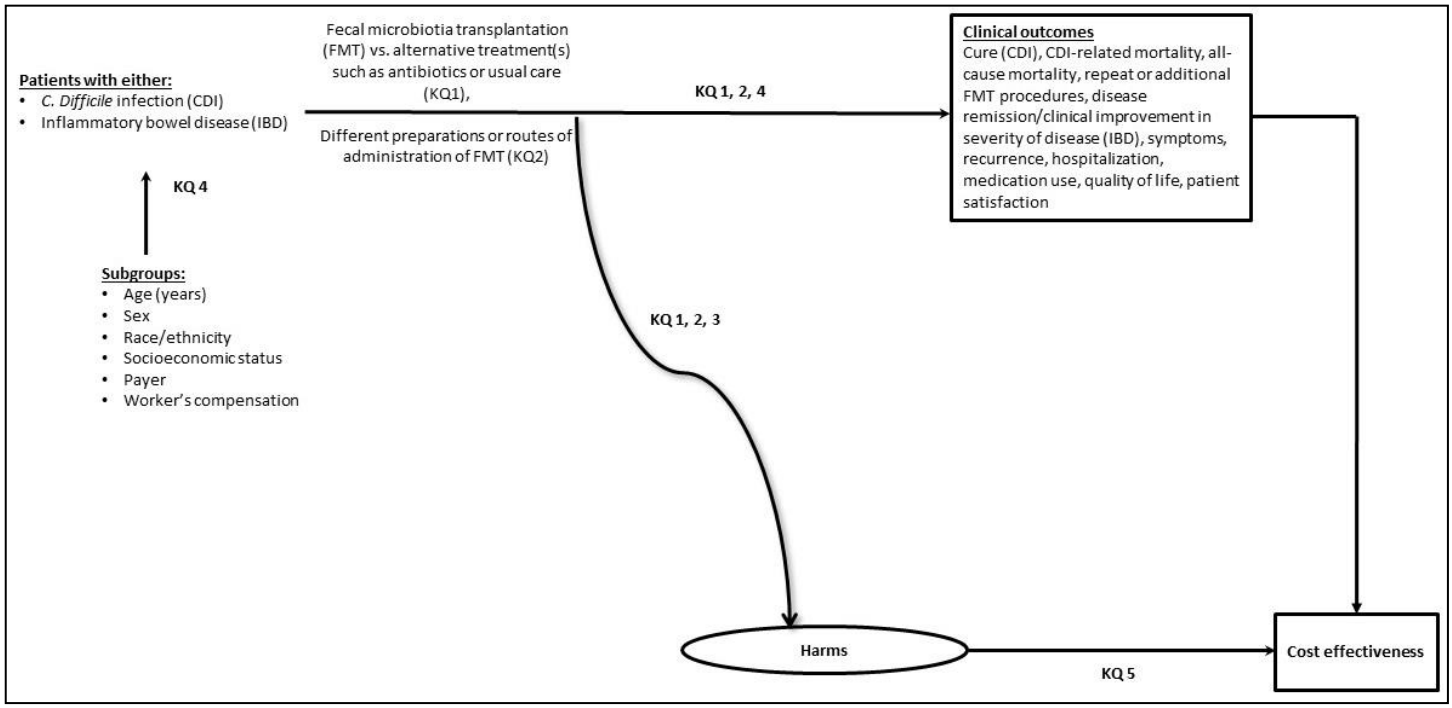
The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of FMT for treating *C. difficile* infections or inflammatory bowel disease (IBD). The differential effectiveness and safety of FMT for subpopulations will be evaluated, as will the cost effectiveness.

1.2 Key Questions

With included conditions (*C. difficile*, inflammatory bowel disease) evaluated separately:

1. What is the evidence of the efficacy and effectiveness of fecal microbiota transplant (FMT)?
2. Does the efficacy and effectiveness of FMT vary by route of administration, timing of administration, or type of preparation (i.e., fresh versus frozen)?
3. What is the evidence of the safety of FMT?
4. Is there evidence of differential efficacy or safety of FMT compared with alternative treatment options in subpopulations? Include consideration of age, sex, race, ethnicity, payer, and worker's compensation.
5. What is the evidence of the cost-effectiveness of FMT compared with alternative treatment options

Figure 1. Analytic framework



1.3 Outcomes Assessed

The studies included in this assessment used a variety of measures to evaluate treatment outcomes, which are outlined in Table 1. The primary outcome measures were those which measured function and pain; these were designated primary outcomes a priori based on clinical expert input. Information on the minimal clinically important difference (MCID) was obtained for the population being evaluated whenever statistical differences were found between groups.

Table 1. Outcome measures used in included studies

Outcome Measure	Assessed By	Components	Score Range	Interpretation
Measures used in CDI studies				
Charlson comorbidity index[29]	Clinician	Each of the following comorbidities assigned a score of 1, 2, 3, or 6; comorbidities are weighted as follows based on their associated mortality risk: • Myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease: each condition present receives score of 1 • Hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma: each condition present receives score of 2 • Moderate or severe liver disease: each condition present receives score of 3 • Metastatic solid tumor, AIDS: each condition present receives score of 6	0-37 (worst)	The higher the score, the higher the patient's risk for mortality based on their existing comorbidities.
Karnofsky performance status[91,140]	Clinician	Interview with patient about dependencies and interactions within existing support networks, placement on a 0-100 scale as follows: • Normal, no complaints, no evidence of disease (score = 100) • Able to carry on normal activity, minor signs or symptoms of disease (score = 90) • Normal activity with effort, some signs or symptoms of disease (score = 80) • Cares for self. Unable to carry on normal activity or to do active work (score = 70) • Requires occasional assistance, but is able to care for most of his needs (score = 60) • Requires considerable assistance and frequent medical care (score = 50) • Disabled, requires special care and assistance (score = 40) • Severely disabled, hospitalization is	0-100 (best)	The higher the score, the higher the patient's performance ability.

Outcome Measure	Assessed By	Components	Score Range	Interpretation
		indicated though death not imminent (score = 30) • Hospitalization necessary, very sick, active supportive treatment necessary (score = 20) • Moribund, fatal processes progressing rapidly (score = 10) • Dead (score = 0)		
Measures used in IBD studies				
Full Mayo Score[114,119]	Patient and Clinician	Each of the following subscales are scored 0-3 (worst): *Stool frequency* • Normal number of stools for this patient (score = 0) • 1 to 2 stools more than normal (score = 1) • 3 to 4 stools more than normal (score = 2) • 5 or more stools more than normal (score = 3) *Rectal bleeding* • No blood seen (score = 0) • Streaks of blood with stool less than half the time (score = 1) • Obvious blood with stool most of the time (score = 2) • Blood alone passes (score = 3) *Findings on endoscopy (Endoscopic Mayo Score)* • Normal or inactive disease (score = 0) • Mild disease (erythema, decreased vascular pattern, mild friability) (score = 1) • Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) (score = 2) • Severe Disease (spontaneous bleeding, ulceration) (score = 3) *Physician's global assessment* • Normal (score = 0) • Mild disease (score = 1) • Moderate disease (score = 2) • Severe disease (score = 3)	0-12 (worst)	The higher the score, the more severe the disease activity.
Inflammatory Bowel Disease Questionnaire (IBDQ)[19,56,61]	Patient	32 Items, each consisting of a 7-point Likert scale (1-7 best). • Social: 5 items • Emotional: 12 items • Bowel: 10 items • Systemic: 5 items	32-224 (best)	The higher the score, the higher the patient quality of life. ≥170 score is remission.

Outcome Measure	Assessed By	Components	Score Range	Interpretation
EQ-5D[28,121]	Patient	5 health states: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression. Each dimension scored: • No health problems (score = 1) • Moderate health problems (score = 2) • Extreme health problems (score = 3) A 5-digit descriptor is produced to represent the level of disability in each of the 5 health states ranging from 11111 to 33333, scored 1-3 (worst) for each health state. An overall health states score is calculated with preferential weights assigned to each health state level (e.g. 21111: 0.85) to obtain a score of 0 to 1.	5-digit descriptor: 11111 to 33333, each digit ranging from 1-3 (worst) Overall health state: 0 (death) to 1 (optimal health)	The lower the score, the greater the disability.
Simple Clinical Colitis Activity Index (SCCAI)[135]	Patient	6 subscales, scored as follows: • Bowel frequency, day (0-3 (worst)) • Bowel frequency, night (1-2 (worst)) • Urgency of defecation (1-3 (worst)) • Blood in stool (1-3 (worst)) • General well-being (0-4 (worst)) • Extracolonic features (1 per manifestation)	0-19+* (worst)	The higher the score, the worse the colitis activity.
Harvey Bradshaw Index[15,57,59]	Patient	5 subscales, scored as follows: • General well-being (0-4 (worst)) • Abdominal pain (0-3 (worst)) • Number of liquid stools per day • Abdominal mass (0-3 (worst)) • Extraintestinal manifestation/complications (can include arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess; score 1 per item)	0-19+* (worst)	The higher the score, the worse the severity of Crohn's disease (more specifically: remission <5, mild disease 5-7, moderate disease 8-16, severe disease >16).
Pediatric Ulcerative Colitis Activity Index (PUCAI)[118,129,130]	Patient	6 subscales, scored as follows: *Abdominal pain* • No pain (score = 0) • Pain can be ignored (score = 5) • Pain cannot be ignored (score = 10) *Rectal bleeding* • None (score = 0) • Small amount only, in less than 50% of stools (score = 10) • Small amount with most stools (score = 20) • Large amount (>50% of the stool content) (score = 30)	0-85 (worst)	The higher the score, the worse the ulcerative colitis. The following categories have been defined: • Remission: <10 • Mild UC: 10-30 Moderate UC: 31-60 • Severe UC: >65

Outcome Measure	Assessed By	Components	Score Range	Interpretation
		Stool consistency of most stools • Formed (score = 0) • Partially formed (score = 5) • Completely unformed (score = 10) *Number of stools per 24 hours* • 0-2 stools (score = 0) • 3-5 stools (score = 5) • 6-8 stools (score = 10) • >8 stools (score = 15) *Nocturnal stools (any episode causing wakening)* • No (score = 0) • Yes (score = 10) *Activity level* • No limitation on activity (score = 0) • Occasional limitation of activity (score = 5) • Severe restricted activity (score = 10)		

CDI: *Clostridium difficile* infection; IBD: Inflammatory Bowel Disease; IBDQ: Inflammatory Bowel Disease Questionnaire; SCCAI: Simple Clinical Colitis Activity Index; PUCAI: Pediatric Ulcerative Colitis Activity Index; UC: Ulcerative Colitis

* Score does not have a defined cap, as one or more subscales does not have a predefined range

1.4 Washington State Utilization and Cost Data

Fecal Microbiota Therapy

Analysis of state utilization data shows low claims volume for this emerging procedure. Given the low volume, participating agency findings are aggregated.

Methods:

State agency programs included:

- PEBB/UMP
- PEBB Medicare
- Labor and Industries
- Medicaid Fee-for-Service
- Medicaid Managed Care

Demographics: No exclusion due to age or gender.

Utilization: Claims between January 2011 and December 2015
Exclusion: Denied claims ($0.00 Allw/$0.00 Paid)

Diagnoses: For individuals receiving FMB therapy:
8.45 Intestinal infection due to Clostridium difficile
A04.7 Enterocolitis due to clostridium difficile

Coding:
44705 Preparation of fecal microbiota for instillation, including assessment of donor specimen
GO455 Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
44799 Unlisted procedure, small intestine
AND
A04.4 or 008.45 Primary or secondary diagnosis Clostridium infection.

Utilization Summary:

Average age: 49 years old

Cost/reimbursement (5 year period)
Per procedure average amount paid (range): $207 to $3, 979. Does not include facility charges.

2. Background

2.1 Epidemiology and Burden of Disease

The intestinal microbiota plays a major role in maintaining a healthy state and is one of the major regulators between the internal and external human environment.[16,38] The gastrointestinal microbiota is comprised of 15,000 to 40,000 bacterial species,[48,49] although only a fraction of these species are found in abundance.[17] The microbiota's symbiotic relationship with the host aids gastrointestinal function,[17,37] and disruption of this homeostasis is associated with gastrointestinal issues such as *Clostridium difficile* infection (CDI) and inflammatory bowel disease (IBD).[38]

Clostridium difficile-associated disease is a leading bacterial cause of diarrhea and is emerging as one of the most significant nosocomial infections, as many infections occur following antibiotic usage and/or hospitalization.[87] The number of CDI diagnoses doubled between the years 2001 and 2005,[10] and it is currently estimated that *C. difficile* infects nearly 500,000 people and causes 15,000 deaths every year in the US, 80% of which occur in persons aged 65 years and older.[26,27]

Inflammatory bowel disease (IBD), which largely consists of Crohn's Disease (CD) and ulcerative colitis (UC), is estimated to affect 0.4% of Western industrialized populations.[46,64] Approximately 700,000 new cases of IBD are diagnosed in the United States each year and as of 2014, 1.6 million Americans were living with IBD; of these cases, an estimated 780,000 are attributed to CD and 907,000 are attributed to UC.[7] Throughout the course of disease, surgery is required in approximately 75% of individuals with CD and in 23% to 45% of individuals with UC.[6] For individuals with CD, 30% of individuals will experience symptom recurrence within three years of surgery and 60% will experience recurrence within 10 years.[6]

The burden of CDI and IBD on the healthcare system and society are considerable. *C. difficile*-related hospitalizations have increased by 237% since 2000.[101] In 2009, the National Institute of Health estimated that 1.9 million ambulatory care visits are due to IBD,[1] with 187,000 of those hospitalizations due to Crohn's Disease and 107,000 hospitalizations due to ulcerative colitis. IBD is estimated to cost $1 billion per year in inpatient costs.[101]

CDI and IBD are the main conditions covered in this report. Details regarding etiology, symptomatology, natural history, and treatment methods for these conditions are provided below.

2.2 Conditions of Interest

2.2.1 *C. difficile infection (CDI)*

C. difficile is a species of bacteria that is Gram-positive and able to form heat-resistant spores; these spores can also be resistant to eradication by commercial disinfectants, making them difficult to eliminate from the

environment.[87] *C. difficile* can be found in the soil, within animals, and on food; in addition, an estimated 5% to 15% of healthy adults, 57% of those residing in long-term care facilities, and as many as 84% of children under the age of two are asymptomatic carriers.[125]

Infection with *C. difficile* typically occurs via fecal-to-mouth transmission,[55,87] although proliferation of existing *C. difficile* populations in the host microbiome can also lead to disease.[87] A diagnosis of CDI requires: (1) sudden onset diarrhea (≥ 3 unformed stools in 24 hours) or documented ileus or toxic megacolon, plus (2) a positive stool test for a toxigenic strain *C. difficile* (or its toxins) or documented pseudomembranous colitis.[10,31,40] Aside from exposure to the bacteria, which most commonly occurs in long-term healthcare facilities and hospitals, the primary risk factor for development of CDI is use of antibiotics (particularly broad-spectrum antibiotics). Antibiotics disturb the normal gut flora, and CDI most commonly impacts patients who have received recent antibiotic treatment.[10] Other risk factors for CDI include hospitalization, older age, diminished gastric acid through proton pump inhibitor use, immunosuppression, feeding through a nasogastric tube, and concurrent disease such as IBD or chronic kidney disease.[10,18,125]

Pathogenic *C. difficile* produces enterotoxin (toxin A) and cytotoxin (toxin B), which cause diarrhea and gastrointestinal inflammation. Other symptoms range in severity and include fever, abdominal pain.[16] If CDI is inadequately treated, dehydration, kidney failure, and death may result.[10,27,31] The infection is typically treated with the antibiotics metronidazole, vancomycin, or fidaxomicin, with metronidazole (and sometimes vancomycin) being first-line antibiotics, vancomycin used for more severe illness, and fidaxomicin typically reserved for recurrent infection.[10] Approximately 20% to 60% of patients have CDI recurrence after antibiotic treatment,[10,27,62] and those who develop multiple recurrences become increasingly resistant to antibiotic treatment.[10] Recurrences can either be reinfection of the original strain or of a new strain.[31] Recurrent CDI can become chronic, persisting for years.[11] Guidelines currently indicate that the antibiotics metronidazole or vancomycin can be used for a first recurrent CDI, but subsequent recurrences or chronic CDI should be treated using vancomycin administered using a tapered and/or pulsed regimen.[31]

2.2.2 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an umbrella term that describes several conditions related to chronic inflammation of the digestive tract. The most common forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD), other forms include collagenous colitis and lymphocytic colitis. UC and CD are differentiated by location of the inflammation: UC is a disease of the mucosa that affects only the colon and rectum, while Crohn's disease is transmural and may affect any part of the digestive system.[38,76,93]

Symptoms of IBD include diarrhea, visible blood in the stool, abdominal pain, fatigue, vomiting, bloating, and weight loss. Severe cases may present with symptoms/signs of toxicity such as fever, tachycardia, anemia, or increased erythrocyte sedimentation rate.[55] Disease onset is typically gradual and followed by periods of remission and relapse to an active disease state.[38] Most cases of CD and UC are diagnosed between the ages of 15 and 35; the median age of diagnosis for UC and CD are 34.9 years and 29.5 years respectively.[7] There is currently no cure for IBD, so treatment focuses on managing inflammation and gastrointestinal symptoms.[46] When medical therapy is not sufficient, surgery to remove affected portions of the digestive tract are necessary.

The etiology of IBD is unknown, but it is thought to result from an abnormal immune response to a change in colonic environment in a genetically susceptible individual.[90] Genetic influences may play a greater role in CD than in UC due to a stronger correlation of disease in twin studies and a larger number of identified susceptible loci.[38] Risk factors for IBD include smoking, diets high in fat and sugar, use of certain medications (NSAIDs, isotretinonin), stress, and high socioeconomic status.[38,39] Additionally, CD occurs twice as frequently as UC in

pediatric populations.[7] Appendectomy has also been associated with an increased incidence for CD (but a decreased incidence of UC).[38,113]

2.3 Technology: Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT)—also referred to as fecal transplantation, fecal bacteriotherapy, fecal flora reconstitution, or stool transplantation—has recently been of great interest to physicians and patients seeking treatment for cases of *C. difficile* infection refractory to antibiotic treatment as well as for IBD-related diseases. Due to the complex nature of the human microbiota, the exact method for how FMT treats CDI or IBD is unclear,[68,84] but it is thought to help restore the microbiota to healthy levels of diversity,[84] as gastrointestinal dysbiosis is thought to be a factor in IBD[54] and CDI[20] pathogenesis.

OpenBiome, a Massachusetts-based stool bank that provides FMT for clinical use,[33] has provided 4,000 treatments for recurrent CDI to 300 clinical sites since its inception in 2013.[115] However, FMT is not currently widely offered, although the material is widely available and inexpensive[11] — as such, there are online communities that exist to guide those who wish to take a do-it-yourself approach to FMT, a unique issue that evades FDA oversight.

In a clinical setting, FMT is derived from donor stool screened for pathogens and transmissible diseases, and is usually delivered in liquid form to the upper or lower gastrointestinal tract. FMT was first noted in the medical literature in 1958 to treat four patients with pseudomembranous enterocolitis via enema.[42] However, it was only in 2013 that the first randomized controlled trial was published investigating FMT for use in patients with recurrent CDI.[131]

2.3.1 Indications

The most accepted use of FMT is for treatment of patients with recurrent or relapsing CDI. Currently, several medical organizations recommend FMT for recurrent CDI that has been non-responsive to oral antibiotic treatment.[11,40,44,89,124] Recurrence can be defined as either three episodes of mild-to-moderate CDI refractory to a six to eight week taper of antibiotics, moderate CDI refractory to antibiotics for at least one week, or severe CDI refractory to antibiotics after 48 hours.[5,11]

The data is much more limited regarding FMT use in patients with IBD, but the available evidence suggests that FMT may be effective for treating active IBD. Reduction or elimination of symptoms as well as cessation of IBD medications was achieved by 76% of included patients in a single systematic review of 17 case reports and case series consisting of 41 patients, over half of whom had ulcerative colitis.[8]

2.3.2 Donor Selection

Currently, there is no evidence to suggest that any particular donor characteristics result in better patient outcomes; as such, screening focuses on risk reduction.[34] Donors' blood and stool are screened for parasites, *C. difficile*, HIV, hepatitis C, and other transmissible diseases,[37] a process that can take several days to weeks.[134] Additionally, the costs of screening can be expensive;[34] OpenBiome's screening costs are a little over $1,000 USD.[22] A list of tests commonly performed for FMT donor screening[11] indicates that the 2016 Medicare Part B national limit cost is $378.86.[120]

Contraindications to donation were outlined by a 2013 consensus guidance from five medical specialty organizations[108] and include antibiotic treatment in the previous three months; a history of intrinsic gastrointestinal illnesses (e.g., IBD, gastrointestinal malignancies or major gastrointestinal surgical procedures);

a history of autoimmune or atopic illnesses; ongoing immune modulating therapy; history of chronic pain syndromes or neurologic, neurodevelopmental disorders; metabolic syndrome; obesity (BMI >30); moderate to severe undernutrition; or a history of malignant illnesses or ongoing oncologic therapy.

The process of donor recruitment can be challenging; an Australian study found only a 10% success rate in finding suitable donors meeting donor criteria similar to that outlined previously.[99] Factors contributing to this low recruitment rate include inability to adhere to donor guidelines due to the inconvenience of long-term donation and the presence of gastrointestinal parasites in healthy asymptomatic donors.
Donor preparation consists of avoidance of allergy-inducing foods in the days leading up to donation, self-monitoring for symptoms of infection (e.g., fever, diarrhea, vomiting) between screening and donation, and the administration of a laxative the night prior to donation.[11]

2.3.3 FMT Procedure

Methods for preparing stool for and administering FMT are not standardized, with many variations reported in the literature. FMT can be prepared from fresh or previously frozen stool, in either liquid homogenate or in freeze-dried encapsulated form. Regarding available forms of stool for FMT, stool-derived frozen capsules and stool substitute transplant therapy are also being researched as alternative, potentially more attractive forms to the more common liquid homogenate. The Massachusetts-based stool bank OpenBiome has started offering capsules for FMT. However, no randomized controlled trials have been conducted assessing the efficacy of the capsule delivery method, although pilot studies have shown that it is efficacious[97] and case series indicate that there are no serious adverse events associated with capsulized feces for treatment of recurrent CDI.[141] Another alternative preparation is a synthetic stool substitute derived from purified intestinal bacterial cultures; it has been shown to lead to remission in two recurrent CDI patients at six months follow-up.[102] However, this synthetic preparation is currently not commercially available.

To prepare the recipient for FMT, the patient is often asked to adhere to a liquid diet and undergo bowel lavage, which flushes the gastrointestinal tract of fecal matter and the abnormal host microbiota, thus priming the gastrointestinal system for optimal uptake of the healthy donor microbiota. However, bowel lavage is not required for patients undergoing FMT via the duodenal route,[142] although the practice has been reported in the literature.[110] If FMT is to be administered via enema or colonoscopy, loperamide administration is optional; if administration is to be done via the nasogastric or nasoduodenal route, a proton pump inhibitor the evening before and morning of the procedure is recommended.[11]

Once the stool has been obtained from the donor, it is advisable to use the sample within 24 hours, although within six hours is preferable. Until usage, the stool should be kept in an airtight container and chilled[11] or otherwise frozen for long-term storage.[17] The FMT infusion is prepared by combining the stool sample with diluent—usually preservative-free normal saline, water, or 4% milk—and homogenizing in a household-grade blender under a fume hood until a liquid slurry consistency is achieved. A systematic review indicated that FMT mixture diluted with water resulted in a higher percentage of resolved cases, but also resulted in a higher percentage of relapses when compared to other diluent such as preservative-free normal saline, yogurt, or milk.[53] After homogenization, as much particulate is filtered from the mixture as possible. It is recommended that the fecal preparation be used immediately, however if combined with glycerol and aliquoted into cryoprotectant tubes, it can be frozen at –80°C for long-term storage.[34] After administration, particularly during colonoscopy, the patient is asked to retain the stool for as long as possible.[5]

FMT can be delivered into the lower or upper gastrointestinal tract. For administration into the lower gastrointestinal tract, colonoscopy or retention enema are used; while nasogastric (NG) tube, nasoduodenal tube, or duodenoscope are used for delivery into the upper gastrointestinal tract.[34] Colonoscopy has the added

benefit of allowing for visual inspection of the colonic mucosa for other gastrointestinal issues,[17,34] but it can be costly. As such, retention enemas offer a reasonable alternative.[65] Data regarding which administration route is most effective for treatment of CDI remains inconclusive. One review indicated that no clear superiority was demonstrated among administration routes,[11] a systematic review indicated that the treatment efficacy between FMT administration for CDI via nasogastric tube versus colonoscopy group was not significant,[104] a randomized controlled trial indicated that nasogastric administration was as effective as colonoscopic administration,[142] and a systematic review indicated that a lower gastrointestinal route (via colonoscopy or enema) seems to be more effective than an upper gastrointestinal route for treatment of CDI.[65]
Smaller volumes are used for nasogastric delivery (25-50 mL) and larger volumes are used for enema or colonoscopic delivery (200-500 mL).[11] A systematic review showed that greater resolution was attained with larger volumes (>500 mL) compared to smaller volumes (<200 mL) of FMT instillation across studies evaluating FMT delivery by enema, colonoscopy, and nasojuenjal routes.[53]

2.3.4 Proposed Benefits

Anticipated outcomes for CDI patients include symptom resolution and no relapse within eight weeks of procedure;[11] ideally, the goal is complete and permanent resolution of disease. Symptom resolution can be defined as absence of clinical symptoms (e.g., diarrhea) or diagnostic confirmation of disease.[53] Testing for cure via absence of toxin is not recommended,[125] as it has been shown that stool can remain toxin A and B positive for as long as 30 days after symptom resolution.[137]

As IBD is a chronic condition, clinical remission is the aim of FMT.[32] Remission of IBD includes clinical remission (absence of symptoms), endoscopic remission (mucosal healing), and deep remission (no symptoms plus mucosal healing).[127] Clinical remission for UC is defined as remission of symptoms and mucosal inflammation as assessed by clinical examination, blood tests, and endoscopic assessment.[43] For CD, clinical remission is defined as a Crohn's Disease Activity Index (CDAI) score <150.[143]

2.3.5 Consequences and Adverse Events

FMT is generally safe in the short term in treating patients with CDI,[18,68] but data is limited since the technology is relatively new in clinical practice.[68] There are few transient adverse events such as fever, diarrhea,[37] abdominal cramping, belching, bloating, nausea, and flatulence.[68] FMT is also well-tolerated in IBD patients. A recent systematic review of 18 studies reported no serious adverse events.[32] With regards to delivery method, case series have reported that upper gastrointestinal bleed[82] and peritonitis[2] are possible adverse events related to nasogastric tube delivery. However, colonoscopies carry the risk of colonic perforation during FMT administration.[34]

2.3.6 FDA Regulation

In 2013, the FDA released guidance classifying feces as a drug; it is currently labeled as an investigational agent.[47] As a result, performing FMT requires an Investigational New Drug (IND) application, with the exception of use for treating recurrent CDI. In such instances, an IND is not required for FMT so long as adequate patient consent is obtained.[69] However, the requirement of an IND application can be time-consuming, and may be a barrier to adaptation of the technology for other conditions where stemming from gastrointestinal dysbiosis, such as IBD.[68]

2.4 Comparator Treatments

2.4.1 Treatment Alternatives for CDI

Metronidazole and vancomycin are first-line antibiotics for the treatment of CDI. Metronidazole is relatively low in cost ($22 for a 10-day regimen[125]) and is generally used for treatment of non-severe disease; vancomycin is utilized for more severe cases ($100-$680 for a 10-day regimen[125]).[12,30,31,125] Vancomycin is currently the only antibiotic approved by the FDA for this indication.[11]

Guidelines indicate that for mild-to-moderate CDI,[40,125] oral metronidazole is strongly recommended. For severe CDI, vancomycin is recommended.[40,125] For severe and complicated CDI, oral vancomycin with intravenous metronidazole is strongly recommended, so long as the patient does not have significant abdominal distention. For a first recurrence of CDI, the same regimen for the initial episode can be used; however, if CDI recurrence is severe, vancomycin should be used. A second recurrence can be treated with a pulsed vancomycin regimen. A Cochrane Review indicated that there was no difference between metronidazole and vancomycin among three studies for the treatment of CDAD in an adult population.[94] Metronidazole, either alone or in conjunction with ciprofloxacin, may be helpful in treatment of CDI.[92] A single placebo-controlled RCT (N=44) found that vancomycin was superior to placebo for the treatment of *C. difficile* associated-diarrhea.[66] A systematic review found that vancomycin alone was not more efficacious than metronidazole, vancomycin combined with fusidic acid, vancomycin combined with nitazoxanide, or vancomycin combined with rifaximin for the treatment of CDAD.[94] Pulsed and/or tapered courses of vancomycin are preferred for CDI treatment over a traditional 10 to 14 day course.[11] However, those who had a tapered course of vancomycin had a recurrence rate of 31% while those who received pulsed dosing of vancomycin had an even lower recurrence rate of 14%.[86]

Other antibiotics utilized include fidaxomicin, which has a lower rate of recurrences compared to vancomycin; a randomized controlled trial found it to be non-inferior for treatment of initial CDI and associated with a lower rate of CDI recurrence.[80] Fidaxomicin is has a moderate strength of recommendation for use in initial CDI,[40] but there are no data regarding its use in severe or complicated CDI.[125] Of note, fidaxomicin has a considerably higher cost than metronidazole or vancomycin, with a 10-day regimen costing approximately $2800.[125] Teicoplanin has been shown to be similarly effective to metronidazole or vancomycin for treatment of *C. difficile* associated-diarrhea,[137] but it is costly and unavailable in the United States.[31,94] Case reports have shown that tigecycline, in conjunction with metronidazole,[81] or vancomycin[58] or vancomycin alone,[58] is beneficial for severe or recurrent CDI,[58,81] but further RCTs are needed to establish its efficacy.[125] The efficacy of surotomycin and cadazolid is still undergoing testing in phase 3 clinical trials for the treatment of CDI.[10]

Approximately 20% to 60% of patients with CDI will have recurrence after antibiotic treatment.[10,27,62] As such, additional medications used to treat CDI include toxin-binding resins and polymers, such as cholestyramine. Cholestyramine is useful for the adsorption of *C. difficile* toxins A and B, as well as the reduction of diarrhea and other symptoms caused by these toxins.[123] There is also limited evidence for adjunctive probiotics (e.g., *Saccharomyces boulardii* and *Lactobacillus rhamnosus)*, which may reduce recurrences in patients with CDI.[40,125,139] Immunotherapy is another option, although guidelines indicate there is little evidence to support their use for treatment of initial or recurrent CDI.[40,125]

2.4.2 Treatment Alternatives for IBD

Antibiotics are commonly administered for the treatment of severe, complicated IBD, but may be used in patients with more mild forms of CD and UC[95] with the rationale that antibiotics eliminate the pathogenic bacteria responsible for exacerbation of symptoms.[116] For fulminant UC (defined as severe painful UC with more than 10 stools per day plus bleeding, distension, and fever), broad spectrum antibiotics (e.g., ciprofloxacin,

metronidazole) in conjunction with intravenous glucocorticoids (e.g., prednisolone) are recommended. Ciprofloxacin is also commonly used to treat perianal complications of Crohn's disease.[92] Broad spectrum antibiotics are also useful for those with mild-to-moderate UC who fail primary treatment with or unable to tolerate 5-aminosalicyclic acid (5-ASA) drugs.[45]

There are a number of additional medications commonly administered to IBD patients. These include 5-ASA drugs, glucocorticoids, and immunosuppressive agents.[45] 5-ASAs are a first-line treatment for mild-to-moderate UC as they are very effective and maintain remission in approximately 75% of patients.[83] Failure of 5-ASA treatment may warrant treatment with cyclosporine or anti-tumor necrosis factor.[83]

Glucocorticoids may help for those with mild-to-moderate disease; administration of prednisone elicits response in 60% to 80% of patients within 10 to 14 days.[45] Non-systemic glucocorticoids (e.g., budesonide) can be useful for first-line therapy, but not for maintenance of remission.[45] The antidiarrheal medications loperamide and cholestyramine can also be useful to ameliorate symptoms.[45]

The evidence is limited for the use of probiotics in IBD-related diseases. A systematic review found there was little good quality evidence for the use of probiotics in CD. [52] However, the use of probiotics for ulcerative colitis was generally beneficial, although the evidence base was disparate regarding populations studied and study methodology.[52]

2.5 Clinical Guidelines

The National Guideline Clearinghouse (NGC), PubMed, Google and Google Scholar, references in other papers, the American College of Gastroenterology website, the American Gastroenterological Association website, and the American Society for Gastrointestinal Endoscopy website were searched for guidelines related to the use of FMT. Key word searches were performed: ("fecal Microbiota transplant" OR "feces transplant" OR "fecal flora transplant") AND ("guide" or "guideline"); ("fecal transplant" OR "fecal Microbiota transplant" OR "fecal implant") AND ("guide" or "guideline"). Eight guidelines were identified that provide recommendations for the use of FMT.

Details of all identified guidelines for the use of fecal microbiota transplantation for treatment of CDI and IBD, including UC and CD, can be found in Table 2.

Guidelines that provided a rating and/or strength of recommendation are briefly summarized below, including guidelines from:

- American College of Gastroenterology
- European Society of Clinical Microbiology and Infectious Diseases
- Public Health England

***Clostridium difficile* Infection (CDI)**

American College of Gastroenterology, 2013: Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections:

- FMT should be considered in patients with a third recurrence of *C. difficile* infection after a pulsed vancomycin regimen.

European Society of Clinical Microbiology and Infectious Diseases, 2014: Update of the Treatment Guidance Document for Clostridium difficile Infection:

- FMT in combination with oral antibiotic treatment is strongly recommended for multiple, recurrent *C. difficile* infections unresponsive to antibiotic treatment.

Public Health England, 2013: Updated Guidance on the Management and Treatment of Clostridium Difficile Infection:

- Donor stool transplant can be considered as one of several treatment alternatives in patients with multiple recurrent *C. difficile* infections with evidence of malnutrition, wasting, etc.

Inflammatory Bowel Disease (IBD)

No full-text guidelines were identified that provided an evaluation of the level of recommendation for the use of FMT in patients with IBD.

Table 2. Summary of Clinical Guidelines

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
American College of Gastroenterology (ACG)[125] 2013 *Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections*	5 case series, 2 case reports, 1 RCT, 1 SR, 4 study type NR	In patients with recurrent *C. difficile*, if there is a third recurrence after a pulsed vancomycin regimen, FMT should be considered.	Conditional recommendation, Moderate-quality evidence*
European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[40] 2014 *European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection*	1 RCT, 22 study type NR	For multiple, recurrent *C. difficile* infections unresponsive to antibiotic treatment, fecal transplantation in combination with oral antibiotic treatment is strongly recommended.	A-I†
The Ohio State University Wexner Medical Center[107] 2014 *Fecal Microbiota Transplant (FMT) for the Treatment of Clostridium difficile Infection*	NR	FMT can be considered for patients with recurring *C. difficile* after ≥2 episodes of mild-to-moderate *C. difficile* and failure to respond to appropriate antimicrobial treatment regimens‡, OR patients with ≥2 episodes of severe *C. difficile* resulting in hospitalization and significant morbidity within 1 year, OR patients with a severe first episode of active *C. difficile* requiring hospitalization and non-responsive to maximal medical therapy.‡ A second FMT may be considered in patients who failed the first FMT treatment.	NR
Public Health England[139] 2013	1 SR, 1 RCT	In patients with multiple recurrent *C. difficile* infections with evidence of malnutrition, wasting, etc., donor stool transplant can be considered as one of several treatment alternatives (including	C§

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
Updated guidance on the management and treatment of Clostridium difficile infection		reviewing all antibiotics and drug therapies, a supervised trial of anti-motility agents alone, fidaxomicin (10-14 days) if not previously received, vancomycin tapering/pulse therapy (4-6 weeks), or IV immunoglobulin).	
National Institute for Health and Care Excellence (NICE)[44] 2013 *Faecal Microbiota transplant for recurrent Clostridium difficile infection: interventional procedure guidance*	1 RCT, 1 SR, 1 comparative cohort	FMT should only be considered for patients with recurrent *C. difficile* infections that have failed to respond to antibiotics and other treatments.	NR

Fecal Microbiota Transplantation Workgroup
(Bakken, Borody, Surawicz et al.)[11]
 	
2011
 	
Treating Clostridium difficile Infection with Fecal Microbiota Transplantation
	NR	FMT may be given to patients who have:
		• Recurrent or relapsing *C. difficile*.
		  ○ ≥ 3 episodes of mild to moderate *C. difficile* and failure of a 6- to 8-week taper with vancomycin with or without an alternative antibiotic (e.g., rifaximin, nitazoxanide).
		  ○ ≥ 2 episodes of severe *C. difficile* resulting in hospitalization and associated with significant morbidity.
		• Moderate *C. difficile* not responding to standard therapy (vancomycin) for at least a week.
		• Severe (and perhaps even fulminant *C. difficile* colitis) with no response to standard therapy after 48 hours.
			NR

New Zealand Society of Gastroenterology[43] 2015 *New Zealand Society of Gastroenterology Guidelines for the Management of Refractory Ulcerative Colitis*	1 meta-analysis of 17 case series/reports, 2 RCTs	There is some evidence that FMT might be a potential effective and safe treatment in ulcerative colitis, but issues such as the most advantageous microflora in the donor stool need to be carefully considered before FMT can be recommended in routine practice.	NR
Canadian Association of Gastroenterology[89]	3 case reports, 5 case series, 1 review	Currently, there is sufficient evidence to recommend FMT in patients with CDI that have failed or had recurrent infection after two rounds	NR

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
2014 *Canadian Association of Gastroenterology position statement: Fecal microbiota transplant therapy*		of different antibiotics (usually metronidazole and vancomycin). This intervention should only be performed by health care practitioners experienced in giving FMT using donors that are healthy and are extensively screened for communicable disease. There is currently insufficient evidence to recommend FMT for patients with IBD and this should only be given in the context of a clinical study. Although not considered here, other potential indications for FMT are not supported by evidence and should only be explored as a part of a research protocol. There is an urgent need to standardize how FMT donors are screened and we recommend that all groups undertaking therapeutic FMT should set up prospective adverse events registries to follow patients in the short and long term.	

ACG: American College of Gastroenterology; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; IV: intravenous; NICE: National Institute for Health and Care Excellence; NR: Not reported; SR: Systematic review

* ACG Strength of recommendation:

Strong = when the evidence shows the benefit of the intervention or treatment clearly outweighs any risk
Conditional = Uncertainty exists about the risk-benefit ratio.

ACG Quality of Evidence:
High = Further research is unlikely to change confidence in estimate of effect.
Moderate = Further research is likely to have an important impact and may change the estimate.
Low = Further research is very likely to change the estimate.

† ESCMID Definition of Strength of Recommendation Grade (ESCMID):
A = Strongly supports a recommendation for use.
B = Moderately supports a recommendations for use.
C = Marginally supports a recommendation for use.
D = Supports a recommendation AGAINST use.

ESCMID Definition of Quality of Evidence (QoE) ESCMID:

I = Evidence from at least one properly designed randomized, controlled trial.
II = Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from more than one center); from multiple time series; or from dramatic results of uncontrolled experiments).
III = Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees.

‡ "Appropriate antimicrobial treatment" and "maximal medical therapy" consist of varying regimens of antibiotic treatment with metronidazole, vancomycin or fidaxomicin.

§ **Public Health England Strength of Evidence:**

Grade A = Strongly recommended and supported by systematic review of RCTs or individual RCTs.
Grade B = Strongly recommended and supported by non-RCT studies and/or by clinical governance reports and/or the Code.
Grade C = Recommended and supported by group consensus and/or strong theoretical rationale.

2.6 Previous Systematic Reviews/Technology Assessments

A total of three Health Technology Assessments (HTAs) and 10 systematic reviews (SRs) were identified regarding FMT administered through enema, colonoscopy, and the nasoduodenal route. HTAs were found by searching PubMed [("fecal microbiota transplant*") OR ("fecal transplant") OR ("fecal bacteriotherapy")) AND "health technology assessment"; "health technology assessment" "fecal" ("transplant" OR "transplants" OR "bacteriotherapy" OR "microbial" OR "microbiota" OR "transfer" OR "transplantation")], the University of York Centre for Reviews and Dissemination database, the NICE Guidance Database, and Google Scholar. SRs were found by searching PubMed using the search strategy described in Appendix B. SRs were included if they were published 2014 or later and met the inclusion criteria as outlined in the PICO table. None of the included HTAs provided a strength of evidence evaluation for their primary conclusions.

Table 3. Previous Health Technology Assessments

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
CADTH 2015[46] Canadian Agency for Drugs and Technologies in Health (CADTH) *Fecal microbiota transplantation (Fecal Transplant) for adults with inflammatory bowel disease*	January 1, 2013 to August 31, 2015	Inflammatory Bowel Disease (IBD) (e.g., Crohn's Disease and ulcerative colitis) without *C. difficile*	FMT vs. water retention enema, autologous stool transplantation, standard therapy	2 SRs (n=234, 2 RCTs (n=123), 1 comparative cohort (n=15), 3 case series (n=42)	**Efficacy** - One SR indicated clinical remission was achieved by 45% of patients over a short f/u; 4/9 studies evaluated followed patients for ≥3 months. Clinical remission for patients with ulcerative colitis was 22% (95% CU: 10.4% to 40.8%) and 61% in patients with Crohn's disease (95% CI: 28.4% to 85.6%) (n=39). - Another SR indicated that in short-term f/u (<3 months), clinical improvement ranged from 0% to 68% in patients with ulcerative colitis or Crohn's disease. - One RCT in ulcerative colitis patients comparing FMT to water-only retention enema indicated that there was significant FMT benefit, with 24% of patients in FMT group achieving clinical remission versus only 5% of those in the placebo group at 7 weeks follow-up. However, the study was terminated at the halfway point because the difference between groups in the primary outcome of clinical remission did not achieve statistical significance. - Another RCT in ulcerative colitis patients comparing donor FMT to autologous transplantation showed no significant difference in rates of clinical remission and endoscopic response at 12 weeks follow-up. This trial was also terminated after a second interim analysis. **Safety** - FMT was well-tolerated and authors reported it as generally safe. Common adverse events included fever, an increase in C-reactive protein (an indication of inflammation in response to infection), diarrhea, and vomiting. However, due to the sparse amount of evidence available to date, experts have questioned the long-term consequences of FMT with regards to infection, cancer, and autoimmune and metabolic diseases. **Economic**	No

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
					NR	
Institute of Health Economics, Alberta STE 2011[55] Canada Fecal transplantation for the treatment of *Clostridium difficile*-associated disease or ulcerative colitis	January 2000 to February 2010	CDAD (8 studies), UC (1 study), and UC complicated by CDAD (1 study)	FMT	10 case series (n=149)	**Efficacy** - Symptoms, most frequently diarrhea, usually improved immediately following the fecal transplantation procedure. However, the improvement or resolution of diarrhea was not always consistent with negative testing for CD toxins. Diarrhea improved in 46% to 100% of patients and resolved in 44% to 96% of patients after fecal transplantation. Data did not demonstrate difference in outcomes based on administration method. (8 case series) - *C. difficile* toxin tests were negative in the majority of patients (further details not provided). (5 case series) **Safety** - Only five out of the 10 included case series reported on adverse events. Most reported that adverse events were not severe (such as sore throat, headache, and gastrointestinal problems), and one study reported a death from peritonitis that was possibly linked to fecal transplantation via a nasogastric tube. **Economic** - No formal cost-effectiveness studies were found in the patient population of interest, but information provided by local clinical experts indicated that the total cost for FMT via rectal retention enema is approximately CAD $500 - $1,500.	No
HealthPACT 2014[126] Australia Fecal microbiota transplantation	NR	Recurrent or refractory CDI; IBD	FMT via enema, nasoduodenal route, colonoscopy	1 RCT, 4 SRs/meta-analyses, 1 case series, 1 cost-effectiveness study (n NR)	**Efficacy** - Three systematic reviews/meta-analyses included an overlapping body of evidence and reached similar conclusions with CDI cure rates varying from 80% to 100%. - One RCT concluded that the addition of FMT to conventional therapy was more effective in treating patients with recurrent CDI than vancomycin, especially among those with multiple relapses of CDI.	No

Assessment (year)	Search Dates	Diagnosis	Treatments Evaluated	Evidence Base Available	Primary Conclusions	Critical Appraisal
					- One SR consisting of case series and reports investigating the efficacy and safety of FMT in gastrointestinal and non-gastrointestinal disorders in adults in children found an overall success rate for IBD in adults of 77.8%. However, the number of patients is too limited to be meaningful. **Safety** - One RCT found that most patients (94%) had diarrhea immediately after infusion, 31% had abdominal cramping and 19% belching. All symptoms resolved within three hours. During follow-up, three patients (19%) reported constipation. No other adverse events related to study treatment were reported. One death that occurred in the vancomycin group was determined to be unrelated to the study drug. **Economic** - A single economic analysis found that FMT via colonoscopy is the most cost-effective method compared to vancomycin, metronidazole, fidaxomicin, and FMT via duodenal infusion and FMT via enema.	

CAD: Canadian dollars; CADTH: Canadian Agency for Drugs and Technologies in Health; CD: Crohn's Disease; CDAD: *Clostridium difficile* associated disease; CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease; NHMRC: National Health and Medical Research Council; NR: not reported; SR: Systematic review

Table 4. Selected Previous Systematic Reviews

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
AHRQ (2016)[23] 2011–2015 MEDLINE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, ICTRP	To update the 2011 review of differences in accuracy of diagnostic tests and the effects of interventions to prevent and treat CDI in adults.	Recurrent or refractory CDI	FMT vs. vancomycin (2 RCTs); colonoscopic vs. nasogastric adminis-tration (1 RCT)	Resolution of diarrhea and recurrence of CDI	3 RCTs, 23 case series for recurrent CDI (N=751); 3 contributing case series* (n=19)	Yes	No	Efficacy Low-strength evidence suggests that FMT may have a significant effect on reducing recurrent CDI incidence. A qualitative analysis of the un-pooled data showed that FMT resolves diarrhea and prevents relapse in people with recurrent CDI. Reported success rates ranged from 48% to 100%, however the evidence is limited by methodological weakness. Evidence for FMT for refractory CDI was insufficient. Safety No conclusions provided. Serious adverse events included one hospitalization, two cases of infections unrelated to FMT, peritonitis, pneumonia, and microperforation of the colon. Upper gastrointestinal bleeding was reported in one study with nasogastric administration of FMT. All-cause mortality after FMT

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								ranged from 0% to 25% when reported, depending on the length of follow-up. It was unclear if deaths were related to FMT. Adverse events after FMT in a single small RCT were diarrhea, cramps, belching and nausea, and constipation. Follow-up for the majority of the studies was three months or less so long-term adverse events are largely unknown.
Bagdasarian (2015)[10] January 1978 to October 2014 Ovid MEDLINE and Cochrane databases	To review current evidence regarding best practices for the diagnosis and treatment of CDI in adults.	Recurrent CDI	Vancomycin for 5 days followed by either 1 or 2 treatments with FMT vs. vancomycin alone for 14 days vs. vancomycin for 14 days plus bowel lavage (1 RCT)	Symptom resolution, adverse events	1 RCT, 3 SRs, 1 case series (N=NR)	No	No	<u>Efficacy</u> FMT is associated with symptom resolution of recurrent CDI, but its role in primary and severe CDI is not established. Two systematic reviews and one RCT found symptom resolution rates of 87% to 94%. A recent feasibility study used frozen fecal capsules to treat 20 patients with recurrent CDI, resulting in a 90% response rate after 1 or 2 treatments. <u>Safety</u> Three SRs did not report any significant adverse events after FMT for refractory or recurrent CDI.

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
Baxter (2016)[13] Database inception to October 2014 MEDLINE and EMBASE	To present the adverse events that have been associated with the use of FMT, as reported in English literature to date.	Recurrent or refractory CDI (n=1190), CDI with IBD (n=13), UC (n=186), CD (n=67), UC pouchitis (n=8), IBD mixed or unspecified (n=4)	Autologous feces vs. donor feces (1 RCT) Donor feces vs. water (1 RCT) Vancomycin, bowel lavage and subsequent infusion of donor feces via nasoduodenal tube vs. vancomycin for 14 days with bowel lavage on day 4-5 vs. vancomycin for 14 days alone (1 RCT)	Adverse events	3 RCTs, 106 case series and case reports† (N=NR)	No	No	Efficacy NR Safety Adverse events appear to be uncommon, often mild and self-limiting; however, serious adverse events including bacteremia, perforations, and death have been reported. In some cases, a credible association was not established due to the lack of controlled data. Three deaths potentially attributable to FMT occurred.
Cammarota (2014)[24] Database inception to February 2013 PubMed, Scopus, ISI Web of Science, and Cochrane Library	To assess the impact of FMT for the treatment of *Clostridium difficile*-associated diarrhea.	Recurrent or refractory CDI	FMT with vancomycin vs. Vancomycin (1 RCT)	Symptom resolution, adverse events	1 RCT, 20 case series, 15 case reports (N=536)	Yes	No	Efficacy In the majority of cases, symptoms improved immediately after the first FMT procedure and patients stayed diarrhea free for several months. Diarrhea resolution rates varied according to site of infusion— however, no conclusions can be drawn because upper and lower routes of administration were not compared head-to-head.

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								Safety Results from included studies suggest that the procedure is safe. No severe adverse events were reported. Overall FMT seems efficacious and safe for the treatment of recurrent CDI. Hospitals should encourage the development of fecal transplantation programs to improve therapy of local patients.
Colman (2014)[32] Varying dates to May 2014‡ EMBASE, MEDLINE, the Cochrane library, Biomed central Cases Database, proceedings from annual meetings of national and international	To evaluate the efficacy of FMT as treatment for patients with IBD.	UC (n=79), Crohn's disease (n=39), IBD unclassified (n=4)	FMT vs. water enema (1 RCT)	Clinical remission, mucosal healing	1 RCT, 9 prospective cohort studies, 8 retrospective case studies (N=122)	Yes	Yes	Efficacy A meta-analysis of cohort studies demonstrated a pooled estimate for achieving short-term clinical remission after FMT of 36.2%. It might appear that FMT is more efficacious in a younger population—however, results are significantly heterogeneous. Safety The evidence suggests that FMT is generally tolerable and safe. Although multiple studies report fever post-FMT, most consider post-administration symptoms

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
gastroenterology conferences (ACG, DDW, AIBD, ECCO, NASPGHAN, ESPGHAN, and the British Society of Gastroenterology annual meeting)								as a consequence of the administration procedures. Studies with longer follow-up are necessary to assess long-term immunologic effects or onset of latent infections.
Drekonia (2015)[41] Database inception to January 2015 MEDLINE, Cochrane Library, and clincialtrials.gov	To assess the efficacy, comparative effectiveness, and harms of FMT for CDI	Recurrent or refractory CDI	FMT via nasoduodenal tube vs. vancomycin vs. vancomycin-plus-bowel lavage (1 RCT) Nasogastric tube vs. colonoscopy (1 RCT)	Resolution of symptoms	2 RCTs, 28 case series, 5 case reports (N=NR)	No	No	Efficacy Low-strength evidence supports FMT as having a substantial effect for adults with recurrent CDI. There is insufficient evidence about FMT for patients with refractory CDI or for initial treatment of CDI. Evidence is insufficient about whether treatment effects vary by FMT donor, preparation, or delivery method. Safety Mild adverse events attributed to FMT were reported including, diarrhea, cramping, transient fever and dizziness. No serious adverse events were directly attributed to FMT. Rare adverse events reported in case reports included abdominal pain

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								and hypotension, herpes zoster, recurrence of *E. coli*, a flare of UC, and two cases of norovirus gastroenteritis. <u>Patient acceptance</u> One RCT suggested that a low enrollment rate of patients at an early stage of recurrence reflected a reluctance to receive FMT at that point. Several case series reported that patients expressed no concern with any aspect of FMT. Among patients surveyed at least 3 months after FMT, 97% indicated that they would be willing to receive FMT in the future.
Furuya-Kanamori (2016)[50] Database inception to August 2015 PubMed, Embase, Cochrane CENTRAL	To compare upper gastrointestinal versus lower gastrointestinal delivery routes of fecal microbiota transplantation for refractory or recurrent/relapsing *Clostridium difficile* infection (CDI)	Recurrent or refractory CDI	Upper (nasogastric tube) vs. Lower (gastroscopy, colonoscopy, enema, ileo-colonoscopy) gastro-intestinal delivery	Time to clinical failure, defined as recurrence or relapse after FMT inter-vention	14 studies, study type NR (N=305)	No	Yes	<u>Efficacy</u> A total of 305 patients were treated with FMT; 208 received FMT via a lower gastrointestinal (LGI) route and 97 received FMT via an upper gastrointestinal (UGI). At 30 and 90 days, the risk of clinical failure was 5.6% and 17.9% in the UGI group compared with 4.9% and 8.5% in the LGI delivery route group, respectively. Time-varying

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								analysis suggested a 3-fold increase in hazard of clinical failure for UGI delivery (hazard ratio, 3.43; 95% confidence interval, 1.32-8.93) in the period after 30 days. Safety No major procedural adverse effects (e.g., bowel perforation or death related to procedure) were reported.
Ianiro (2014)[60] Varying dates to January 2014§ PubMed, SCOPUS, ISI Web of Science, the Cochrane Library, bibliographies of relevant articles, and records from the following yearly symposia: United European Gastroenterology,	To perform a systematic review of the literature on the use of fecal microbiota transplantation in inflammatory bowel disease	UC (n=44), UC + pouchitis (n=8), UC + CDI (n=25), Crohn's disease (n=22), Crohn's disease + CDI (n=31), unidentified IBD (n=2), unidentified IBD + CDI (n=1) CDI was recurrent or refractory	NR	Frequency of symptoms, endoscopic assessment	8 open-label trials, 23 case reports or case series (N=133)	Yes	No	Efficacy Limited and weak evidence reported a resolution or reduction in symptoms in 71% of patients with evaluable IBD. Safety Serious adverse events, such as bacteremia and transient relapse of previously quiescent UC were reported in patients with IBD undergoing FMT for CDI. The most common adverse events related to the feces infusion were high fever, a temporary increase in CRP, diarrhea, and vomiting.

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
Digestive Disease Week, ECCO Congress, and CCFA Annual Scientific Meeting								
Li (2016)[79] Database inception to September 2015 MEDLINE, Cochrane Library, and EMBASE	To evaluate the long-term (≥ 90 days) efficacy and safety of fecal microbiota transplantation for *C. difficile* infection and explore the factors affecting the fecal microbiota transplantation outcomes	Recurrent or refractory CDI	NR	Primary cure rate, recurrence	3 retro-spective cohort studies, 2 prospective case series, 13 retro-spective case series (N=NR)	Yes	Yes	Overall Limited and marginally biased evidence seems to find FMT to be a highly effective and robust therapy for recurrent CDI. Efficacy Pooled analysis showed a primary cure rate of 91.2%. The primary cure rate of younger (<65 years) individuals was significantly higher than that of older (≥65 years) individuals. There was no significant difference between early and late recurrence rates. The early recurrence rate of young individuals was significantly lower than that of older individuals. The primary cure rate of the lower gastrointestinal route group was significantly higher than the upper route. There was no statistically significant difference in the overall recurrence rate, early

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								recurrence rate and late recurrence rate between upper and lower gastrointestinal administration route groups. The primary cure rate of patient-related donors was lower than that of random healthy donors, although statistically insignificant. The overall recurrence, early recurrence and late recurrence rates of patient-related donors were higher than that of random healthy donors, but the associations were also insignificant. <u>Safety</u> In total, 38 deaths were reported, although the relation of death and FMT ranged from unrelated to possibly related. Gastrointestinal symptoms were the most commonly reported adverse event and almost all of these symptoms were short-lived, moderate, and manageable. Other adverse events included low-grade and self-limiting fever and

SR, Search dates	Purpose	Condition	Comparison	Primary Outcomes	Evidence Base	Risk of Bias Assessed	Quantitative Synthesis	Primary Conclusions
								emerging diseases such as septicemia, pneumonia, peritonitis, peripheral neuropathy, Sjogren's disease, idiopathic thrombocytopenic purpura, and rheumatoid arthritis.
Rossen (2015)[110] Varying dates to July 2013** MEDLINE, EMBASE, the Cochrane Library, and conference proceedings from ECCO, UEGW, ECCMID, IDSA, DDW, and ACG	To study the clinical efficacy and safety of FMT as clinical therapy.	Recurrent or refractory CDI (33 case studies, 1 RCT), IBD (7 case studies)	Fecal intestinal microbiota infusion vs. autologous microbiota infusion (1 RCT); FMT preceded by a short regimen of vancomycin and bowel lavage vs. standard vancomycin regimen vs. standard vancomycin and bowel lavage (1 RCT)	Resolution of diarrhea in CDI, proportion of patients free from relapse, clinical remission and/or clinical improve-ment in UC and CD	1 RCT, 40 case studies (N=NR)	Yes	No	<u>Efficacy</u> FMT is highly effective in CDI, and holds promise in UC. Evidence is too limited to draw conclusions about the use of FMT for the treatment of CD. <u>Safety</u> FMT was accompanied by mild, self-limiting gastrointestinal symptoms in the majority of patients. Transient fever was reported in 11 patients, all of whom had either CD or UC. Two possible FMT-related deaths occurred: one patient died from aspiration during sedation for FMT and one severely ill CDI patient died of a peritonitis that could be related to treatment.

ACG: American College of Gastroenterology; AHRQ: Agency for Healthcare Research and Qualtiy; AIBD: Advances in IBD; AMED: Allied and Complementary Medicine; CCFA: Crohn's and Colitis Foundation of America; CD: Crohn's Disease; CDI: *Clostridium difficile* infection; CRP: C-reactive protein; DDW: Digestive Diseases Week; ECCMID: European Congress of Clinical Microbiology and Infectious Diseases; ECCO: European Crohn's and Colitis Organization; ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition; IBD: Inflammatory Bowel Disease; IBS: irritable bowel syndrome; ICTRP: International Clinical Trials Registry Platform; IDSA: Infectious Diseases Society of America; ISI: Institute for Scientific Information; NASPGHAN:

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not reported; SR: systematic review; UC: Ulcerative Colitis; UEGW: United European Gastroenterology Week

* Unclear if these case series are also represented in the 23 case series listed previously.

† Number of studies reported is for entire report; it is not clear which studies pertain to FMT.

‡ Databases searched from inception to May 2014, conference proceedings searched manually from 2010 through May 2014.

§ Databases searched from inception to January 2014, conference proceedings searched manually from varying dates (United European Gastroenterology 2008-2013; Digestive Disease Week 2001-2013; ECCO 2007-2012; CCFA 2003-2013)

**Databases searched from inception to July 2013, conference proceedings searched manually from varying dates (ECCO 2009-2013; UEGW 2010-2013; ECCMID 2012-2013; IDSA 2003-2012; DDW 1979-2013; ACG 2010-2013)

2.7 Medicare and Representative Private Insurer Coverage Policies

Individual payer websites, the Centers for Medicare and Medicaid Services (CMS) website, and Google were searched for coverage decisions on the use of FMT for the treatment of CDI and IBD. Policy plans were identified from eight payers, three of which are national payers. Coverage policies are consistent and generally support coverage of FMT for recurrent, relapsing, and/or refractory CDI but not for IBD or other pathologies, generally only covering CDI.

Coverage decisions are summarized briefly below and policy details are provided in Table 5.

Centers for Medicare Service (CMS): National Coverage Determination for Blood-Derived Products for Chronic Non-Healing Wounds
There are currently no National Coverage Decisions published from the Centers for Medicare and Medicaid services.

Aetna: Fecal Bacteriotherapy
Aetna covers the use of fecal bacteriotherapy medically necessary for treatment of persons with positive test-confirmed *Clostridium difficile* infection recurrence after two courses of adequate antibiotic therapy, but its use is considered investigational for all other indications.

Cigna: Fecal Bacteriotherapy
Cigna covers the use of FMT for the treatment of recurrent or refractory *Clostridium difficile* infections which meet required criteria, but considers its use for all other indications to be investigational.

EmblemHealth: Fecal microbiota transplantation for Recurrent Clostridium difficile infection
EmblemHealth covers the use of FMT for the treatment of recurrent *Clostridium difficile* infections, given that the individual is on their third recurrence, have failed pulsed vancomycin treatment, and are not immunocompromised.

HealthNet: National Medical Policy: Fecal Bacteriotherapy
HealthNet considers FMT to be medically necessary for recurrent, relapsing, moderate, and severe *Clostridium difficile* infections. For all other indications, including Crohn's disease and inflammatory bowel disease, HealthNet considers the use of FMT to be investigational.

HealthPartners: Fecal Microbiota Transplant
HealthPartners covers FMT for the treatment of recurrent, relapsing, moderate, and severe *Clostridium difficile* infections.

PriorityHealth: Fecal Microbiota Transplantation/ Fecal Bacteriotherapy
PriorityHealth covers FMT for the treatment of recurrent, relapsing, moderate, and severe *Clostridium difficile* infections.

Regence Blue Cross Blue Shield & Regence Blue Shield: Fecal Microbiota Transplantation Medical Policy Manual & Fecal Microbiota Transplant Medicare Advantage Policy Manual
Regence considers FMT to be medically necessary for recurrent Clostridium difficile infections. For all other indications, Regence considers FMT to be investigational.

Table 5. Overview of payer technology assessments and policies

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale/ comments
Centers for Medicare and Medicaid Services (CMS)	NA	NA	None	There are currently no National Coverage Decisions published from the Centers for Medicare and Medicaid services.
Aetna *Fecal Bacteriotherapy* POLICY #: 0844 Last review: 12/22/2015 Next review: 10/21/2016	2000-2011	FMT for CDI: 1 RCT 7 Case series 1 Clinical guideline	Aetna considers fecal bacteriotherapy, including capsulized FMT, medically necessary for persons with positive stool test-confirmed *C. difficile* infection, that has recurred following at least two courses of adequate antibiotic therapy, defined as >10 days of vancomycin at ≥125 mg 4x/day or metronidazole ≥500 mg 3x/day. Aetna considers fecal bacteriotherapy experimental and investigational for all other indications including, but not limited to: • Crohn's disease • Idiopathic thrombocytopenic purpura • Inflammatory bowel syndrome • Insulin resistance • Irritable bowel syndrome • Metabolic syndrome • Multiple sclerosis • Ulcerative colitis	CPT codes covered if criteria met: 44705 HCPCS codes covered if criteria met: G0455 ICD-10 Codes covered if criteria met: A04.7 ICD-10 codes not covered for indications listed in the CPB: D69.3 E88.81 G35 K50.00-51.919 K52.0-K52.9 K58.0-K58.9
Cigna *Fecal Bacteriotherapy* POLICY #: 0516 Last review: 09/15/2015 Next review: 09/15/2016	NR	FMT for CDI: 1 RCT 5 SRs 5 Clinical guidelines FMT for Inflammatory Bowel Disease: 1 SR	Cigna covers FMT for recurrent or refractory *C. difficile* infections when there is failure, intolerance, or contraindication to conventional medical management and all of the following criteria are met: • Diagnostic testing confirms a diagnosis of *C. difficile* infection; • Therapy with the inciting antimicrobial agent(s) has been discontinued where possible; and • Recurrent or persistent episodes of diarrhea following completion of three established	CPT codes covered if medically necessary: 44705 HCPCS codes covered if medically necessary: G0455

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale/ comments
			antibiotic treatment regimens of which two included oral vancomycin. Cigna considers FMT to be investigational for all other indications.	
EmblemHealth *Fecal microbiota transplantation for Recurrent Clostridium difficile infection* POLICY #: MG.MM.ME.49v2 Last review: 06/15/2015 Next review: NR	NR	FMT for CDI: 4 studies, type NR	EmblemHealth covers FMT for recurrent *C. difficile* infection if the individual is on their third recurrence, have failed pulsed vancomycin treatment, and are not immunocompromised.	ICD-9 codes: 008.45 ICD-10 codes: A04.7 CPT codes: 44705 HCPCS codes: G0455

HealthNet
 	
National Medical Policy: Fecal Bacteriotherapy
 	
POLICY #: NMP519
 	
Last review: 11/2014
Next review: NR
	NR	FMT for CDI:
		3 RCTs
		4 SRs
		1 Case report
		5 Clinical guidelines
		6 studies, type NR
			HealthNet considers FMT to be medically necessary for the following indications:
			• Recurrent or relapsing *C. difficile* infection defined as:
			  ○ ≥3 mild to moderate episodes and failure of a 6 to 8 week taper with vancomycin with or without alternative antibiotic; OR
			  ○ ≥2 episodes resulting in hospitalization associated with significant morbidity.
			• Moderate *C. difficile* infection not responding to standard therapy for at least a week.
			• Severe or fulminant *C. difficile* colitis with no response to standard therapy for 48 hours.
			
			HealthNet considers FMT to be investigational for all other indications, including Crohn's disease and inflammatory bowel disease.
				ICD-9 codes: 008.45
				
				ICD-10 codes: A04.7
				
				CPT codes: 44705
				
				HCPCS codes: G0455

HealthPartners *Fecal Microbiota Transplant*	NR	FMT for CDI: 3 studies, type NR	HealthPartners covers FMT for the following indications: • Recurrent or relapsing *C. difficile* infection	NR

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale/ comments
POLICY #: F001-01 Last review: 04/08/2013 Next review: 04/2015			defined as: ○ ≥3 mild to moderate episodes and failure of a 6 to 8 week taper with vancomycin with or without alternative antibiotic; OR ○ ≥2 episodes resulting in hospitalization associated with significant morbidity • Moderate *C. difficile* infection not responding to standard therapy for at least a week. • Severe or fulminant *C. difficile* colitis with no response to standard therapy for 48 hours. HealthPartners does not cover FMT for any other indications.	
PriorityHealth *Fecal Microbiota Transplantation/ Fecal Bacteriotherapy* POLICY #: 91603-R1 Last review: 11/2015 Next review: NR	NR	FMT for CDI: 4 studies, type NR	PriorityHealth covers the use of FMT (FMT)/fecal bacteriotherapy for the following indications: • Recurrent or relapsing C. difficile infections defined as: ○ ≥3 mild to moderate episodes and failure of a 6 to 8 week taper with vancomycin with or without alternative antibiotic; OR ○ ≥2 episodes resulting in hospitalization associated with significant morbidity • Moderate C. difficile infections not responding to standard therapy for at least a week. • Severe or fulminant C. difficile colitis with no response to standard therapy.	ICD-10 codes covered when criteria is met: A04.7 CPT/HCPCS codes: 44705; G0455; 44799
Regence Blue Cross Blue Shield (Oregon and Utah) & Regence Blue Shield (Idaho and select counties of Washington) *Fecal Microbiota Transplantation Medical Policy Manual* POLICY #: 154	NR	FMT for Recurrent *Clostridium difficile* Infections: 4 SRs 2 RCTs 4 Non-randomized studies 1 Clinical guideline FMT for Inflammatory	Regence considers FMT to be medically necessary for recurrent *C. difficile* infections. Regence considers FMTs to be investigational for all indications other than *C. difficile* infections.	CPT codes: 44705 HCPCS codes: G0455

Payer (Year)	Lit search dates	Evidence base available	Policy	Rationale/ comments
Fecal Microbiota Transplant Medicare Advantage Policy Manual POLICY #: M-MED154 Last review: 01/2016 Next review: NR		Bowel Disease: 2 SRs		

BCBS: Blue Cross Blue Shield; BS: Blue Shield; CDI: Clostridium difficile infections; CMS: Center for Medicare and Medicaid Services; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; ICD: International classification of diseases; NA: not applicable; NR: not reported; SR: systematic review

3. The Evidence

3.1 Methods of the Systematic Literature Review

3.1.1 Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of FMT for treating *C. difficile* infections or inflammatory bowel disease (IBD). The differential effectiveness and safety of FMT for subpopulations will be evaluated, as will the cost effectiveness.

3.1.2 Key Questions

With included conditions (*C. difficile*, inflammatory bowel disease) evaluated separately:

1. What is the evidence of the efficacy and effectiveness of fecal microbiota transplantation (FMT)?
2. Does the efficacy and effectiveness of FMT vary by route of administration, timing of administration, or type of preparation (i.e., fresh versus frozen)?
3. What is the evidence of the safety of FMT?
4. Is there evidence of differential efficacy or safety of FMT compared with alternative treatment options in subpopulations? Include consideration of age, sex, race, ethnicity, payer, and worker's compensation.
5. What is the evidence of the cost-effectiveness of FMT compared with alternative treatment options?

3.1.3 Inclusion/exclusion criteria

Inclusion and exclusion criteria are summarized in Table 6. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

Population: Patients undergoing therapeutic treatment for *Clostridium difficile* infection or inflammatory bowel disease (including ulcerative colitis and Crohn's disease)

Intervention: Fecal microbiota transplantation (FMT)

Comparators: Alternative treatment(s) (e.g., antibiotics, disease-specific medication, bowel lavage), different types of fecal preparations (e.g., fresh versus frozen), different routes of administration (e.g., nasoduodenal vs. colonoscopic)

Outcomes: Cure (CDI) (primary), death from CDI (primary), repeat or additional FMT procedures (primary), all-cause mortality (primary), disease remission/clinical improvement in disease severity

(IBD) (primary), symptoms, recurrence, hospitalization, medication use, quality of life, patient satisfaction, adverse events (primary). Excluded from the scope: non-clinical and intermediate outcomes (e.g., gut microflora characteristics, biomarkers of disease).

Study design: Eligible studies compared FMT with an included comparator treatment utilizing a randomized or cohort study design. In the absence of sufficient comparative studies, case series of at least 30 patients (or 10 patients for case series of pediatric patients) were considered to provide context on the primary outcomes. For Key Question 3, case series specifically designed to evaluate harms/adverse events were considered. Only RCTs that stratified results by patient characteristics of interest so that statistical interaction (effect modification) could be evaluated were considered for Key Question 4; subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. For Key question 5, formal economic analyses were eligible for inclusion (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies).

Table 6. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Patients undergoing therapeutic treatment for conditions in which FMT use is currently clinically indicated: • *Clostridium difficile* (*C. difficile*) infection • Inflammatory bowel disease (including ulcerative colitis and Crohn's disease)	• Pregnancy • Conditions in which FMT use is investigational (e.g., obesity, metabolic syndrome, slow transit constipation)
Intervention	Fecal microbiota transplantation (FMT)	
Comparator	• Alternative treatment(s) (e.g., antibiotics, bowel lavage) • Different types of fecal preparations (i.e., fresh versus frozen) • Different routes of administration (i.e., nasoduodenal vs. colonoscopic)	
Outcomes	• Cure (CDI) (primary) • Death attributed to CDI (primary) • Repeat or additional FMT procedures (primary) • All-cause mortality (primary) • Disease remission/clinical improvement in disease severity (IBD) (primary) • Symptoms • Recurrence • Hospitalization • Medication use • Quality of life • Patient satisfaction • Adverse events (primary)	• Non-clinical or intermediate outcomes (e.g., gut microflora characteristics, biomarkers of disease)
Study Design	**Focus will be on studies with the least potential for bias.** **Key Questions 1-3:** • Randomized controlled trials (RCTs) • High quality non-randomized comparative studies • High quality non-comparative studies (case series) will be considered in the absence of sufficient comparative studies	• Indirect comparisons • Incomplete economic evaluations such as costing studies • Case reports

Study Component	Inclusion	Exclusion
	Key Question 3: • KQ3: High-quality non-comparative studies (case series) designed specifically to evaluate harms/adverse events. **Key Question 4:** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest. **Key Question 5:** • Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Studies in which <80% of patients have a condition of interest
Publication	• Studies published in English in peer reviewed journals or publically available FDA reports	• Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

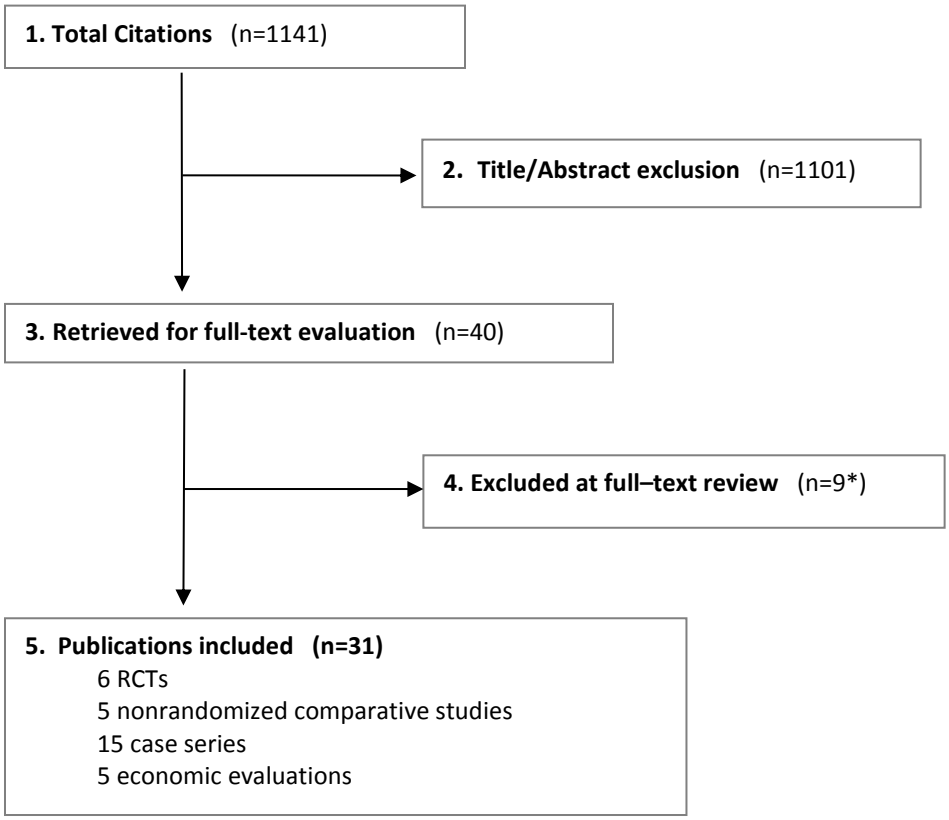
CDI: *Clostridium difficile* infection; IBD: Inflammatory Bowel Disease; KQ: key question

3.1.4 Data sources and search strategy

Electronic databases were searched from their inception through April 27, 2016. Electronic databases searched included PubMed, EMBASE, and AHRQ for eligible studies, including health technology assessments (HTAs), systematic reviews, and primary studies. The search strategies used for PubMed are shown in Appendix B; hand-searching was also conducted. Figure 2 shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed with reason for exclusion in Appendix C.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. All possible relevant articles were screened using titles and abstracts in stage two. This was done by one to two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Figure 2. Flow chart of literature search results



*Studies listed with reason for exclusion in Appendix C.

3.1.5 Data extraction

Reviewers extracted the following data from the studies included to address Key Questions 1-3: study design, country, number of patients enrolled, inclusion and exclusion criteria, intervention details, type of donor feces used, route of administration, details on repeat treatment, length of follow-up, rate of follow-up, co-interventions, patient characteristics (age, sex, duration of symptoms, baseline pain and function scores), length of follow-up, patient demographics, study funding, clinical efficacy or effectiveness outcomes (cure (for CDI), death attributed to CDI (for CDI patients), repeat or additional FMT procedures, all-cause mortality, disease remission/clinical improvement (for IBD patients), symptoms, recurrence, hospitalization, medication use, quality of life, patient satisfaction), safety outcomes (adverse events, harms, complications), and differential efficacy or safety outcomes for any subgroup. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. Detailed study and patient characteristics is available in Appendix F; results from the comparative studies are available in the results section of this document while those from the case series are in Appendix G.

3.1.6 Quality assessment: Overall Strength of evidence (SoE), Risk of Bias, and QHES evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by

the Oxford Centre for Evidence-based Medicine,[103] precepts outlined by the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) Working Group,[9] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[138] Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[96] Details of the risk of bias and QHES methodology are available in Appendix D. Based on these quality criteria, each study chosen for inclusion for a Key Question was given a risk of bias (or QHES) rating; details of each study's rating with reasons for not given credit when applicable are available in Appendix E. Standardized abstraction guidelines were used to determine the risk of bias (or QHES) rating for each study included in this assessment. Observational studies were considered to have been conducted retrospectively unless clearly stated otherwise.

The strength of evidence for the overall body of evidence for all critical health outcomes was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ).[14] The strength of evidence was based on the highest quality evidence available for a given outcome. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results that are similar in terms of range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes.
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing.

Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those comprised entirely or primarily of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association). Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

3.1.7 Analysis

Evidence for different conditions was analyzed separately. The primary outcome measures were those which measured disease status (cure for CDI and remission for IBD), mortality, and the need for additional FMT procedures; these were designated primary outcomes a priori based on clinical expert input. The definitions of CDI cure and IBD remission were obtained from the studies reporting these outcomes.

An attempt was made to pool results when there were two or more RCTs of similar quality and which employed similar interventions and outcome timing/interpretation. However, because of differences in study quality, RCTs were not pooled with nonrandomized studies. For all dichotomous outcomes, risk differences (RD) and their respective 95% confidence intervals (CI) were calculated to compare the rate of occurrence between treatments. For those dichotomous outcomes that could be pooled, risk differences and figures were produced using Review Manager v5.2.6 and the difference within each study was weighted and pooled using the Mantel-Haenszel method. For those dichotomous outcomes that could not be pooled, risk differences were calculated using the Rothman Episheet (www.krothman.org/episheet.xls).

For all continuous outcomes, mean differences (MD) and their respective 95% confidence intervals were calculated. There were no instances where continuous outcomes data could be pooled.

4. Results

Number of studies retained

For Key Questions 1, 2, and 3, six randomized trials, five cohort studies, and 15 case series were included. The comparisons evaluated and their respective studies are listed in Table 7; comparisons of interest not listed in the table below had no comparative evidence available that met the inclusion criteria. In addition, five economic evaluations were included, all of which evaluated the comparative impact of FMT in CDI patients. The selection of the studies are summarized in Figure 2.

Table 7. Number of studies included.

Comparisons	Studies
***C. difficile* Infection (CDI)**	
FMT vs. antibiotics	2 RCTs[25,35,105,106,128,131], 1 prospective cohort study[74]
Colonoscopic vs. Nasogastric FMT	1 RCT[142]
FMT after 2 vs. ≤3 CDI recurrences	1 retrospective database study[136]
FMT using frozen vs. fresh feces	1 RCT[78], 1 retrospective cohort study[117]
FMT (noncomparative)	13 case series[4,21,51,63,67,70,72,77,85,98,100,111,112]
Inflammatory Bowel Disease (IBD)	
FMT vs. placebo infusion	2 RCTs[90,109]
FMT (noncomparative)	2 case series[36,73]

CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease

4.1 Key Question 1: Efficacy and effectiveness of FMT compared with alternative treatments

4.1.1 Clostridium difficile Infection (CDI)

4.1.1.1 FMT vs. Antibiotics for CDI

Studies included

Two RCTs (Cammarota 2015[25], van Nood 2013[131]) compared FMT to antibiotics in patients with recurrent CDI. In addition, one prospective cohort study (Lagier 2015[74]) compared FMT (given for the first CDI episode only) to antibiotics (given for the first episode or up to two relapses of CDI) in patients infected with a particularly virulent strain of *C. difficile* (ribotype CD027).

Efficacy: FMT vs. Antibiotics for Recurrent CDI

RCT characteristics

Both trials were small, enrolling 39 and 43 patients each. Both were conducted in Europe, open-label, and found to be at moderately low risk of bias. Detailed patient and study characteristics are available in Table 8 as well as in Appendix Table F1.

Inclusion criteria and patient characteristics: Patients in both studies had experienced at least one relapse of CDI following appropriate antibiotic treatment (vancomycin ≥125 mg 4x/day for ≥10 days, or metronidazole 500 mg 3x/day X ≥10 days). CDI was diagnosed by the presence of diarrhea (loose or watery stools ≥3 times per day for ≥2 consecutive days, or ≥8 times within previous 2 days) plus stool that tested positive for *C. difficile* toxin. In both studies, the median number of CDI recurrences at baseline was three (range, 1-9), and the median daily number of bowel movements was five to six. Patients who had prolonged immunodeficiency, were taking antibiotic (other than for CDI) or vasopressor medication at baseline, had less than three months' life expectancy, were in the intensive care unit or were pregnant (for van Nood only) were excluded.

Treatments: Both trials randomized patients to FMT plus bowel lavage (following a short course of vancomycin) or to vancomycin (standard course). One of the trials (van Nood) had a third arm, which consisted of vancomycin (standard course) plus bowel lavage. Because the majority of patients had previously failed vancomycin therapy (56% (van Nood) and 90% (Cammarota)), the trials were comparing in many cases a failed treatment to a novel treatment. In both studies, the FMT group underwent bowel lavage on the last day of antibiotics; FMT was performed the following day using fresh donor feces that had been collected within six hours (range of means, 3.1-3.9 hours) of the procedure. Donor feces were transplanted via the nasoduodenal (van Nood) or colonoscopic (Cammarota) route. Donors had been screened for a number of pathogens and were under the age of 50[25] or 60[131] years; one trial[25] stated a preference towards selecting relatives or friends of the patient as donors and additionally placed a restriction on donors who had taken antibiotics in the six months prior. No additional co-interventions were reported. Patients received allocated treatments with one exception: in the van Nood trial[131], one patient in the FMT group was not able to receive FMT at the start of the study due to rapidly declining health in the immediate post-randomization period (patient developed poor renal graft function); the patient was instead treated with vancomycin.

Treatment failure protocol: Upon CDI recurrence after the initial FMT, patients were offered repeat FMT: feces from a different donor was used in one trial (van Nood); the other trial (Cammarota) repeated FMT every 3 days until resolution was achieved. (Note that the procedure in the latter trial was a deviation from the study protocol; this change was made after the first two patients who received FMT had relapse five days following the first or second procedure, were not given an additional FMT (one was treated with vancomycin according to the original protocol, the second was in too poor of health to undergo the procedure), and died within one to two weeks.) Patients in the vancomycin (± bowel lavage) group who had CDI recurrence were handled differently between the two trials: while the van Nood trial offered FMT off-protocol to these patients following recurrence of CDI, the Cammarota trial

did not treat control group patients with FMT (and no treatment details for these patients were reported).

Risk of bias: Both trials were found to be at moderately low risk of bias (Appendix Table E1). Although patients were not blinded to treatment received in either trial, one trial (van Nood) employed a blinded adjudication committee to evaluate cure. Methodological limitations included failure to report intention-to-treat analyses (van Nood- one FMT patient was excluded from analysis after deviation from the protocol), lack of blinded outcome assessment (Cammarota), differential follow-up between groups (Cammarota had 100% vs. 84% follow-up for the FMT vs. vancomycin groups), and failure to control for potentially confounding differences in baseline characteristics (van Nood had a number of imbalances in baseline characteristics that weren't controlled for, including mean age, sex, Charlson comorbidity index, previous failure of antibiotic treatment). Neither trial was industry-funded.

Table 8. CDI RCTs comparing FMT to Antibiotics: Study and Patient Characteristics

	Cammarota 2015		van Nood 2013		
	FMT + bowel lavage (n = 20)	Vancomycin (n = 19)	FMT + bowel lavage (n = 17)*	Vancomycin (n = 13)	Vancomycin + bowel lavage (n = 13)
Patient demographics					
Females, %	60% (12/20)	58% (11/19)	50% (8/16)	54% (7/13)	23% (3/13)
Age, years; mean ± SD (range)	71 (29-89)	75 (49-93)	73 ± 13	66 ± 14	69 ± 16
Recurrences of CDI; median (range)	3 (2-5)	3 (1-4)	3 (1-5)	3 (1-4)	2 (1-9)
Stool frequency/ 24 hours; median (range)	6 (2-15)	6 (2-12)	5 (3-20)	5 (3-12)	5 (3-10)
Prior tapered vancomycin therapy, %	95% (19/20)	84% (16/19)	62% (10/16)	62% (8/13)	46% (6/13)
Days of antibiotic use for CDI since initial diagnosis; mean ± SD	NR	NR	63 ± 41	51 ± 27	49 ± 38
Antibiotic use prior to CDI, %	100% (20/20)	100% (19/19)	100% (16/16)	92% (12/13)	100% (13/13)
Hospital-acquired CDI, %	50% (10/20)	74% (14/19)	62% (10/16)	46% (6/13)	77% (10/13)
Admitted to hospital at inclusion, %	75% (15/20)	84% (16/19)	31% (5/16)	31% (4/13)	31% (4/13)
Admitted to ICU within previous month, %	NR	NR	6% (1/16)	0% (0/13)	8% (1/13)
Feeding tube present, %	NR	NR	19% (3/16)	15% (2/13)	15% (2/13)
Use of proton pump inhibitor	55% (11/20)	68% (13/19)	81% (13/16)	77% (10/13)	85% (11/13)
Charlson comorbidity index (0-37 (worst)) (median (range))	2 (0-5)†	2 (1-5)†	3 (0-4)	1 (0-8)	1 (0-6)
Karnofsky performance status (0-100 (best)), (mean ± SD‡):	NR	NR	50 ± 18	50 ± 17	56 ± 21

	Cammarota 2015		van Nood 2013		
	FMT + bowel lavage (n = 20)	Vancomycin (n = 19)	FMT + bowel lavage (n = 17)*	Vancomycin (n = 13)	Vancomycin + bowel lavage (n = 13)
Procedural characteristics					
Patient blinded to treatment received	No		No		
Antibiotics	Short-course of vancomycin (125 mg orally 4x/day X 3 days)	Standard-course of vancomycin (125 mg orally 4x/day X 10 days) and then a pulse regimen for ≥3 weeks (125-500 mg every 2-3 days	Short-course of vancomycin (500 mg orally 4x/day X 4-5 days)	Standard-course of vancomycin (500 mg orally 4x/day X 14 days)	Standard-course of vancomycin (500 mg orally 4x/day X 14 days)
Bowel lavage?	Yes (day before FMT)	No	Yes (day before FMT)	No	Yes (on day 4 or 5)
Donor feces	Fresh (time from collection to infusion ≤6 (mean 3.8 ± 0.8) hours)), mixed with saline	NA	Fresh (time from collection to infusion ≤6 (mean 3.1 ± 1.9) hours)), mixed with saline	NA	NA
Route of administration	Colonoscopic	NA	Nasoduodenal	NA	NA
Repeat treatment	Upon infection recurrence (repeat with initial treatment; for FMT, repeat every 3 days until resolution)		Upon infection recurrence FMT offered (in FMT group, feces from different donor used)		
Cross-over during study f/u period	0%	0%	0%	0%	0%
Co-interventions	None reported		None reported		
Length (%) f/u	10 weeks from end of last treatment (100% (39/39)); Through 8 months (for mortality only) (92% (36/39))		10 weeks from end of last treatment (98% (42/43));		
Country	Italy		The Netherlands		
Funding	Catholic University of Rome		Grant (The Netherlands Organization for Health Research and Development)		
Risk of bias	Moderately Low		Moderately Low		

CDI: *Clostridium difficile* infection; ICU: intensive care unit; NR: not reported; SD: standard deviation

*van Nood: One FMT patient was excluded from the study but re-included in our analysis because sufficient details were provided to do so. This patient was excluded by the study due to protocol deviation (patient became too ill to receive FMT, was treated with vancomycin instead, and had a recurrence 41 days after end of vancomycin treatment, then treated with

FMT and cured) but was included in our analysis (as failure). Details on patient: the patient was a renal transplant recipient (transplantation had occurred 11 months prior to randomization), and experienced a rapid decrease in renal-graft function immediately after randomization; the nephrologist recommended the patient not receive FMT at that time and was given vancomycin instead.

†Cammarota indicated the score ranged from 0-100 (higher=better) but the reported scores don't appear to be on a 0-100 scale; we assumed this was an error and that the outcome measure was calculated as described in Table 1.

‡van Nood: the study indicated that these scores were medians, however medians were otherwise reported with ranges and the table containing the data is footnoted to indicate that scores were reported as mean ± SD.

Efficacy Results

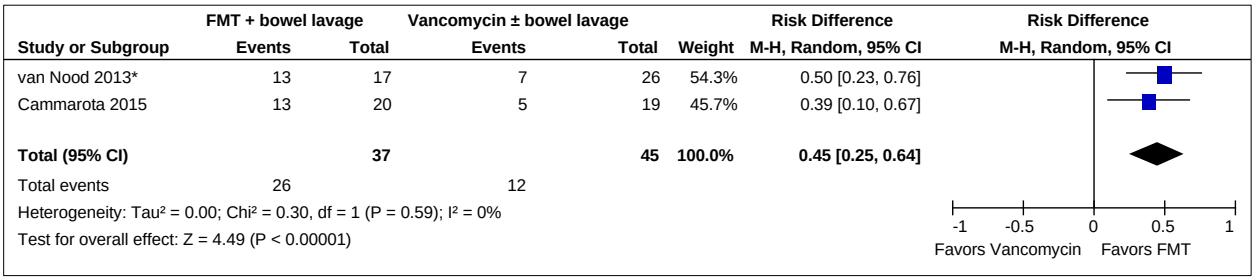
For the van Nood trial, results from the two control groups (vancomycin alone; vancomycin plus bowel lavage) were combined because all reported outcomes were similar between the two groups.[131] Both trials were terminated early following interim analysis that demonstrated considerably better cure rates with FMT versus vancomycin (with or without bowel lavage).[25,131]

Cure

Cure was the primary outcome in both trials and was defined as the absence of recurrent CDI (CDI-related diarrhea (as defined above) plus two[25] or three[131] negative stool tests for *C. difficile* toxin). Diarrhea was recorded with a stool diary, and toxin tests were performed at predefined time points or whenever diarrhea occurred. The length of follow-up was slightly different between the trials, with van Nood[131] measuring cure 2.5 months from the initiation of treatment and Cammarota[25] doing so 2.5 months from the end of treatment.

After a single treatment, significantly more FMT patients achieved cure through 2.5 months than those in the vancomycin group (pooled RD 45% (95% CI 25%, 64%)) (Figure 3). Cure following additional treatments is discussed in the section on additional procedures (below).

Figure 3. CDI RCTs comparing single FMT to Antibiotics: Cure through 2.5 months of initial treatment.



*van Nood: One FMT patient was excluded from the study but re-included in our analysis because sufficient details were provided to do so (see footnote in Table 8).

CDI recurrence details

For the patients who did not achieve cure, the following information was provided. In the van Nood trial[131], 4/17 FMT patients did not achieve cure following the initial treatment (which was FMT in 3 and vancomycin in 1 patient (the latter received vancomycin only as described above due to health limitations)); all four had CDI recurrence and underwent an additional FMT procedure. In vancomycin groups of the van Nood trial, 19/26 patients did not achieve cure following the allocated treatment; 18 of these patients had CDI recurrence and underwent FMT, and one died at day 13 from severe heart

failure and chronic pulmonary disease. In the Cammarota trial[25], 7/20 FMT patients had CDI recurrence, six of whom underwent one to three additional FMT infusions, and one of whom died from CDI-related complications at day 15. In the vancomycin group of the Cammarota trial, 14/19 patients failed to achieve cure following the initial treatment, all had recurrence. The authors did not offer FMT to these patients, and treatment details for these CDI recurrences was not reported.

Details on additional procedures and mortality are provided in the following sections.

Additional procedures:
The protocol for CDI recurrence was difference between the two trials (see "Treatment failure protocol" section above).

In the van Nood trial[131], FMT was offered in both groups upon CDI recurrence. Significantly fewer patients in the FMT group underwent this additional procedure compared with patients in the vancomycin group (24% (4/17) vs. 69% (18/26), RD -46% (95% CI -73%, -19%)) (Table 9). Cure without relapse through 10 weeks of these additional procedures was achieved in 3 patients in the FMT group and in 15 patients in the vancomycin group (following one procedure in 11 patients and two procedures in 4 patients).

In the Cammarota trial, FMT was offered for CDI recurrence only in the FMT group; 30% (6/20) of the FMT group underwent one or more additional FMT procedures after relapse of CDI. Cure was achieved in five of these patients (following one to three additional procedures given every three days). No details were provided on treatment offered to patients in the vancomycin group who had CDI recurrence.

Table 9. CDI RCTs comparing FMT to Antibiotics: Additional FMT procedure for CDI recurrence

Study	F/U	FMT + bowel lavage % (n/N)	Vancomycin ± bowel lavage % (n/N)	RD (95% CI)*	p-value*
van Nood 2013	NR	24% (4/17)†	69% (18/26)	-46% (-73%, -19%)	0.0038
Cammarota 2015	≤10 weeks‡	30% (6/20)	Not offered	NC	NC

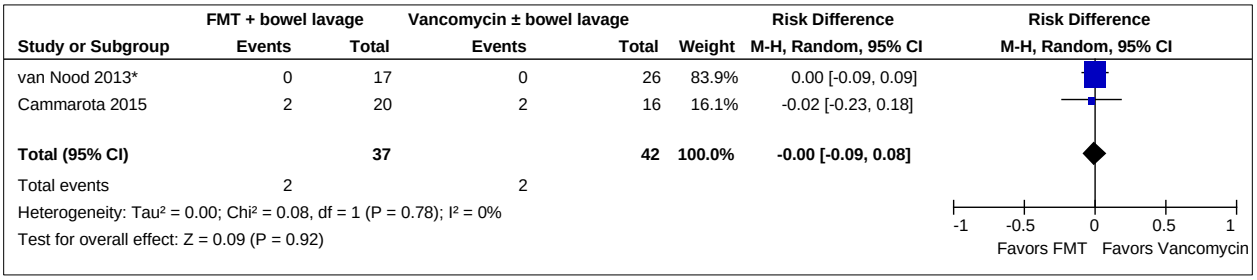
CI: confidence interval; F/U: follow-up; NC: not calculable; RD: risk difference
*Calculated
†van Nood: One FMT patient was excluded from the study but re-included in our analysis because sufficient details were provided to do so (see footnote in Table 8).
‡≤10 weeks from the last treatment given

Mortality:
Mortality attributed to CDI:
Pooled results suggest no difference in mortality attributed to CDI within 2.5 months of treatment (pooled RD 0% (95% CI -9%, 8%)) (Figure 4).[25,131]

In the Cammarota trial[25], there were two CDI-related deaths in each treatment group. In the FMT group, both of the patients who died had initial symptom improvement following FMT, but symptoms returned within five to seven days, and the patients died approximately 19 and 20 days after the initial FMT procedure. One patient was determined to be too ill at the time of recurrence to undergo a second FMT and so was treated with vancomycin and died from sepsis and pulmonary edema two weeks later; the

patient was noted to have had severe cardiomyopathy. Another FMT patient underwent a second fecal infusion but after some symptom resolution had another recurrence after five days, was then treated with vancomycin, and died from sepsis one week later. In the vancomycin group, two patients did not respond to the antibiotic and died from complications attributed to CDI; no other details were reported. There were no deaths attributed to CDI in the van Nood trial[131].

Figure 4. CDI RCTs comparing FMT to Antibiotics: Mortality attributed to CDI within 10 weeks of first treatment.



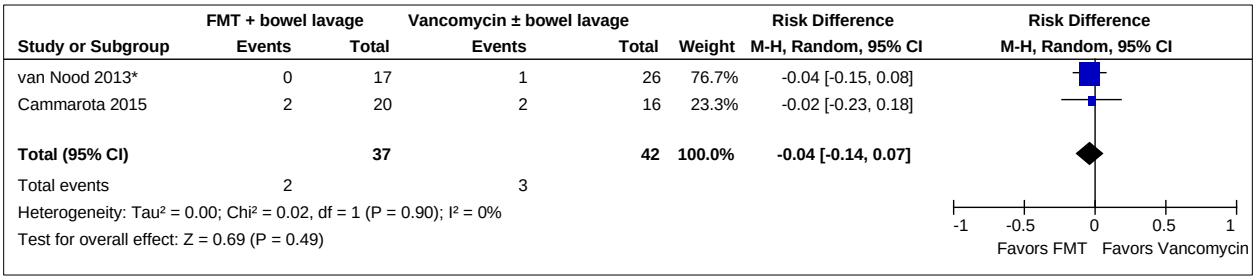
*van Nood: One FMT patient was excluded from the study but re-included in our analysis because sufficient details were provided to do so (see footnote in Table 8).

All-cause mortality:

The pooled effect estimate suggests no difference between FMT and vancomycin groups in all-cause mortality through 2.5 months (RD -4% (95% CI -14%, 7%)) (Figure 5).

In the van Nood trial[131], no deaths occurred in the FMT group, and one death occurred in the vancomycin alone group through 10 weeks: the patient began vancomycin treatment at the hospital, but once home stopped all medication due to severe heart failure and chronic pulmonary disease; the patient died 13 days post-randomization. In the Cammarota trial[25], all deaths through 10 weeks were attributed to CDI (see section above for details).

Figure 5. CDI RCTs comparing FMT to Antibiotics: All-cause mortality through 10 weeks.



*van Nood: One FMT patient was excluded from the study but re-included in our analysis because sufficient details were provided to do so (see footnote in Table 8).

The Cammarota trial[25] additionally tracked all-cause mortality through eight months post-discharge. While fewer patients in the FMT died through this time period compared with the vancomycin group (15% (3/20) vs. 38% (6/16)), the difference did not reach statistical significance due to small sample size (RD -23% (95% CI -51%, 6%)). In the FMT group, there were three deaths total: two attributed to CDI

(see section above for details) and one at eight months that was attributed to a heart attack. In the vancomycin group, a total of six patients died- two attributed to CDI (see section above for details) and four occurred three to eight months post-discharge: the cause of death was known in two patients (severe heart failure (1 patient, death at 6 months), prostate cancer (1 patient, death at 8 months)) and unknown in two patients (death occurred at 3 and 5 months, neither patient had experienced full resolution of CDI but the CDI status at time of death was not known).

Other outcomes

No additional clinical efficacy outcomes were reported.

Effectiveness: FMT vs. Antibiotics for CDI

Nonrandomized comparative study characteristics

One prospective cohort study (Lagier 2015)[74] at moderately high risk of bias met the inclusion criteria. Detailed information on patient and study characteristics are available in Appendix Table F1.

This study compared FMT given for the first CDI episode to antibiotics given for the first one to three CDI episodes. Patients hospitalized with CDI of a specific ribotype (CD027) (associated with a particularly high early mortality rate) were eligible for inclusion.

Patients treated between March and November 2013 formed the control group ("non-early transplantation") and were treated with antibiotics (metronidazole, vancomycin, and/or fidaxomicin) for the first three infections; those with three or more relapses underwent FMT. Of the 45 patients in this group, 93% (42/45) received antibiotics only, while 7% (3/45) ultimately underwent FMT; whenever possible, data are reported for the subset of 42 patients who received antibiotics only. Patients treated in December 2013 or later received "early FMT" (i.e., performed during the first week following diagnosis) via the nasogastric route plus antibiotics for the initial CDI infection (n=16). By design, the patients enrolled in the early FMT group had experienced only one CDI infection, while those in the control group had experienced anywhere from one to four (or more) CDI infections, the mean number of which was not reported. Thus patients in the early FMT group may have been in better overall health than those in the control group due to the number of infections experienced. The mean age was 84 years in both groups, and the early FMT group had fewer males than the control group (13% vs. 43%). Other baseline characteristics (including the simplified Acute Physiology Score, as well as the percentage of patients with malignancy, diabetes, or AIDS) were similar between groups. The study was found to be at moderately high risk of bias due to a number of methodological limitations, including unclear blind outcome assessment, lack of information regarding co-interventions, and failure to control for confounding (Appendix Table E1). The study was conducted in France. Complete follow-up was available in all but two control group patients (so 96% follow-up overall); the duration of follow-up was unclear.

CDI Comparative Effectiveness Results

Cure

Cure was referred to as "avoidance of relapse", which was diarrhea (>3 watery stools per day) plus a stool test positive for CDI 027 ribotype toxin. Following a single FMT, 63% (10/16) of patients in the early FMT group achieved cure through 30 days; relapse data were not reported for the control group (Table 10).[74]

Additional procedures

All six patients in the early FMT group who had relapse after the initial procedure underwent a second infusion and had complete symptom resolution. In the control group, 7% (3/45) ultimately underwent

FMT after experiencing three or more CDI recurrences (per protocol), two of which died (at post-FMT days 28 and 54); the outcome of the third patient was not reported.[74]

Mortality:

Mortality attributed to CDI:

None of the three deaths that occurred in the early FMT group were attributed to CDI. For the control group, it was unclear which deaths were attributed to CDI.[74]

All-cause mortality:

Through one month follow-up, global mortality was significantly lower in the early FMT group compared with those patients in the control group that received only antibiotics group (6% (1/16) vs. 58% (23/40), p<0.001) (Table 10). (Among the control group patients who underwent FMT after three or more CDI recurrences, two died (at post-FMT days 28 and 54)). [74]

Through the entire study period (the duration of which was unclear), patients in the early FMT group had a lower incidence of all-cause mortality compared with those who received only antibiotics (19% (3/16) vs. 64% (27/42), p=0.0021) (Table 10). In the early FMT group, deaths occurred at days 20, 37, and 166; the causes of death were not reported. In those who only received antibiotics, 17 died within the first week post-diagnosis, and 23 died within the first month; the causes of death were not reported.

Other outcomes

No additional clinical effectiveness outcomes were reported.

Table 10. CDI Cohort Study comparing FMT to Antibiotics: All outcomes

Study	Outcome	F/U	FMT % (n/N)	Antibiotics % (n/N)	p-value*
Lagier 2015	Cure† following single FMT	1 month	62.5% (10/16)	NR‡	NA
	CDI-related mortality	Entire study period (duration NR)	0% (0/16)	NR	NA
	All-cause mortality	1 month	6% (1/16)	58% (23/40)	<0.001
		Entire study period (duration NR)	19% (3/16)§	64% (27/42)	0.0021

F/U: follow-up; NA: not applicable; NR: not reported

*Calculated.

†Cure was referred to as "avoidance of relapse"; relapse was defined as diarrhea (defined by >3 liquid stool by day) and positivity for CD027 as diagnosed by the Xpert C. *difficile* Epi PCR assay.

‡All 6 patients that relapsed underwent a second FMT after which all symptoms resolved.

§Died at days 20, 37, and 166; none had clinical signs of *C. difficile* infection.

4.1.1.2 FMT for CDI: Case Series

Because relatively few comparative studies have been published to date, case series with at least 70% follow-up and 30 patients (or 10 patients if in a pediatric population) were considered for inclusion in order to provide additional context on primary outcomes.

A total of 13 case series[4,21,51,63,67,70,72,77,85,98,100,111,112] (2 of which were specific to pediatric patients[72,112]) met the inclusion criteria. Treatment indication was recurrent, severe, and/or complicated CDI in all studies, and sample size ranged from 32 to 229 patients (expect for in the two case series of pediatric patients, which both enrolled 10 patients). FMT was performed using various approaches; additional study details are available in Appendix Table F6.

Cure

Detailed cure results from the case series are available in Appendix Table G1. When defined as an absence of CDI-related diarrhea plus a negative stool test (for CDI or its toxin), cure was achieved in 92% to 94% of patients through two or three months of a single FMT as reported by two studies (Table 11).[70,85] In addition, one of these studies reported that 74% of IBD patients with recurrent CDI achieved this outcome through two months.[70]

When defined as an absence of CDI-related diarrhea, cure following a single FMT was achieved in 48% to 91% of patients (median, 78%) as measured through 1 to 24 months as reported by the nine remaining case series.[4,21,51,63,67,77,98,100,111] Cure rate is reported for different follow-up periods in Table 11. In addition, both studies of pediatric patients reported cure in 90% of patients s evaluated between one and 48 months after a single FMT.[72,112]

Table 11. FMT Case Series for patients with CDI: Cure

Outcome	F/U (range)	Median (range)	Number of studies	Total N (range)
Cure (no diarrhea + negative stool test)	2-3 mos.	93% (92-94%)	2	N=299 (43-229)
Cure (no diarrhea)	1 mos.	87%	1	N=30
	2-3 mos.	79% (52-91%)	6	N=479 (30-146)
	6 (& 24) mos.	48%	1	N=94
	26 mos. (median)	69%	1	N=32

CDI: *Clostridium difficile* infection; F/U: follow-up; NA: not applicable; NR: not reported; RD: risk difference

*Calculated.

Additional procedures

Additional FMT procedures were performed in 0.7% to 48% of patients as reported by 10 studies[4,21,51,63,67,77,85,98,100,111]; cure was subsequently achieved in 67% to 100% of these patients. In the two studies of pediatric patients[72,112], one additional FMT procedure was performed in 0% to 10% of patients (i.e., 1 patient needed repeat FMT); cure was not achieved in this patient. Detailed results are available in Appendix Table G2.

Mortality:

Mortality attributed to CDI:

CDI-related mortality occurred in 0% to 6% (median, 0%) of adult patients as reported by seven case series.[4,51,67,77,85,98,111] Detailed results are available in Appendix Table G3.

All-cause mortality:
Death from any cause (including CDI) was reported in 0% to 21% (median, 6%) of patients by nine case series.[4,21,51,67,77,85,98,100,111] Detailed results are available in Appendix Table G3.

4.1.2 Inflammatory Bowel Disease (IBD)

4.1.2.1 FMT vs. Placebo for IBD

Studies included
Two RCTs (Moayyedi 2015[90], Rossen 2015[109]) compared FMT to placebo treatment in patients with inflammatory bowel disease (IBD), specifically ulcerative colitis (UC). No nonrandomized comparative studies were identified. To provide additional context on primary outcomes, two case series evaluating FMT for IBD were included.

Efficacy
RCT characteristics
Both trials were small, enrolling 75 and 48 patients each, and employed a double-blind, placebo-controlled design. Both trials were terminated early due to futility. One trial was found to be at low risk of bias (Moayyedi) while the other was considered to be at moderately high risk of bias (Rossen). Detailed patient and study characteristics are available in Table 12 as well as in Appendix Table F2.

Inclusion criteria and patient characteristics: Only adults with active UC without an infectious cause (i.e., concomitant *C. difficile* infection or other enteric pathogen) were eligible. Active UC was defined as an endoscopic Mayo Clinic score ≥1 plus a Mayo Clinic score of at least 4 (Moayyedi) or a Simple Clinical Colitis Activity Index (SCCAI) score between 4 and 11 with diagnosis confirmation according to the Lennard-Jones criteria (Rossen). Patients were allowed to continue concomitant treatments for UC (e.g., mesalamine, glucocorticoids, immunosuppressive therapy; anti-tumor necrosis factor (TNF) use was allowed in one trial (Moayyedi) and not permitted in the two months prior by the other trial (Rossen)) as long as the patients had been receiving stable dosages prior to inclusion (for at least 2 (Rossen) or 3 months (Moayyedi)) and the disease remained active. Exclusion criteria included antibiotic or probiotic use within four to six weeks of enrollment, disease severity that required hospitalization, and pregnancy; for Rossen 2015, patients who had used methotrexate in the prior two months or cyclosporine within the previous one month, who had a history of colectomy, a current stoma, or a life expectancy of less than 12 months were also excluded.

Treatments: One trial (Moayyedi) randomized patients to FMT or to placebo (water); both groups received infusion via retention enema once per week for six weeks. In the second trial (Rossen), patients were randomized to undergo FMT via nasoduodenal tube with either donor feces or autologous feces; bowel lavage was performed the evening before and morning of the FMT procedure. The procedure was repeated three weeks after the first. To preserve blinding, patients in both groups donated feces the morning of treatment. FMT was performed using fresh feces in one trial (Rossen) or either fresh (n=15) or frozen (n=21) donor feces in the other trial (Moayyedi). In both trials, stool was used or processed within five to six hours of collection. Donors in both trials had been screened for a number of pathogens and were ineligible to donate if they had taken antibiotics within two (Rossen) or three (Moayyedi) months of screening. Fifteen donors with a mean age of 27 years provided stool samples for one trial (Rossen 2015) while the second trial included six donors (mean age not reported), one of which provided the majority of the stool use for transplantation; donors were primarily anonymous in both trials. No additional co-interventions were reported.

Risk of bias: One trial (Moayyedi) was found to be at low risk of bias and met all the methodological criteria for a good quality RCT. The other trial (Rossen) was considered to be at moderately high risk of bias; methodological limitations included lack of information regarding random sequence generation and concealed allocation, failure to report intention-to-treat analyses (two patients in the FMT-donor group were excluded after randomization and not accounted for), a follow-up rate of less than 80% at 1.5 months (but not at 3 months), and failure to control for potentially confounding differences in baseline characteristics (including median disease duration, extent of disease (e.g., pancolitis), concomitant drug therapy used, median SCCAI score, and Mayo endoscopic score). Detailed information on risk of bias ratings can be found in Appendix Table E2

Table 12. Ulcerative colitis RCTs comparing FMT to Placebo: Study and Patient Characteristics

	Moayyedi 2015		Rossen 2015	
	FMT (n = 38)	Placebo (n = 37)	FMT + bowel lavage (n = 23)	Placebo + bowel lavage (n = 25)
Patient Demographics				
Females, %	53% (20/38)	30% (11/37)	52% (12/23)	56% (14/25)
Age, years; mean ± SD (range)	42.2 ± 15.0	35.8 ± 12.1	40 (33-56)*	41 (30-48)*
Disease duration, years; mean ± SD	7.9 ± 5.6	7.0 ± 6.8	7 (0.27)*	9 (0.27)*
Pancolitis, %	63% (20/36)	38% (12/30)	30% (7/23)	56% (14/25)
Primary sclerosing cholangitis, %	NR	NR	4% (1/23)	4% (1/25)
Mayo endoscopic score, %				
Mayo 1 (mild)	NR	NR	17% (4/23)	8% (2/25)
Mayo 2 (moderate)	NR	NR	48% (11/23)	64% (16/25)
Mayo 3 (severe)	NR	NR	35% (8/23)	28% (7/25)
Site of disease, %				
Rectum only	NR	NR	17% (4/23)	8% (2/25)
Left side of colon	NR	NR	61% (14/23)	68% (17/25)
Proximal to splenic flexure	NR	NR	22% (5/23)	24% (6/25)
Concomitant medication				
Any	NR	NR	91% (21/23)	72% (18/25)
Mesalamine therapy	55% (21/38)	54% (20/37)	65% (15/23)	60% (15/25)
Glucocorticoids	39% (15/38)	35% (13/37)	22% (5/23)	20% (5/25)
Mesalamine/glucocorticoid rectal	NR	NR	22% (5/23)	28% (7/25)
Immunosuppressants	29% (11/38)	16% (6/37)	30% (7/23)	32% (8/25)
Anti-TNF therapy	13% (5/38)	5% (2/37)	30% (7/23)†	28% (7/25)†
Loperamide	NR	NR	9% (2/23)	0% (0/25)
Mayo endoscopic score, %				
Mayo 1	NR	NR	17% (4/23)	8% (2/25)
Mayo 2	NR	NR	48% (11/23)	64% (16/25)
Mayo 3	NR	NR	35% (8/23)	28% (7/25)
Full Mayo Clinic Score (0-12 (worst)); mean ± SD	8.2 ± 2.6 (n=38)	7.9 ± 2.3 (n=37)	NR	NR

	Moayyedi 2015		Rossen 2015	
	FMT (n = 38)	Placebo (n = 37)	FMT + bowel lavage (n = 23)	Placebo + bowel lavage (n = 25)
IBDQ score (32-224 (best)); mean ± SD	130.3 ± 36.3 (n=37)	134.4 ± 32.3 (n=37)	NR	NR
EQ-5D score (0-100 (best))§; mean ± SD	75.7 ± 20.4 (n=36)	78.2 ± 15.4 (n=37)	NR	NR
SCCAI score (0-19+ (worst)); median (range)	NR	NR	10 (5-11)	8 (4-11)
Procedural characteristics				
Patient blinded to treatment received	Yes		Yes	
Bowel lavage?	No		Yes (the evening before and the morning of FMT)	
Donor feces	Fresh (n=15), frozen (n=20) or both (n=1)‡; time from collection to processing ≤5 hours, 50 g mixed with water	NA	Fresh; time from collection to infusion ≤6 hours, 60 g mixed with saline	
Placebo	NA	Water 50 ml	NA	Autologous FMT (identical collection and preparation as in donor FMT group)
Route of administration	Retention enema		Nasoduodenal	
Repeat treatment	Per protocol, treatment given 1x/week for 6 weeks		Per protocol, 2nd identical treatment (including bowel lavage) given 3 weeks following the 1st treatment	
Cross-over during study f/u period	0%	0%	0%	0%
Co-interventions	None		None	
Length (%) f/u	7 weeks (95%)	7 weeks (92%)	6 and 12 weeks (71% and 75%)	6 and 12 weeks (80% and 84%)
Country	Canada		Netherlands	
Funding	Academic and charity organizations		Grants	
Risk of bias	Low		Moderately high	

EQ-5D: EuroQol 5 dimension; FMT: fecal microbiota transplantation; f/u: follow-up; IBDQ: Inflammatory Bowel Disease Questionnaire; NA: not applicable; NR: not reported; SCCAI: simple clinical colitis activity index; SD: standard deviation; TNF: tumor necrosis factor.

*Median (interquartile range).

†Indicates prior anti-TNF therapy. Use of anti-TNFs within the 8 weeks prior to enrollment was an exclusion criteria.

‡One patient received both fresh and frozen stool on different weeks.

§The standard EQ-5D score range is 11111-33333, with each digit representing one of five health states, and higher scores indicating worse health. The resulting score can be used to calculate an overall health state with preferential weights

assigned to each health state level (e.g. 21111: 0.85) to obtain a score of 0 to 1. It is not clear how Moayyedi et al. derived a score range of 0-100.

Efficacy Results

Due to variation in the definition of primary outcomes, differing lengths of follow-up and differences in study quality, results were not pooled across the two trials.[90,109] Both trials were terminated early following interim analyses made by Data Monitoring and Safety Committees that showed an observed treatment effect of much less than expected per protocol. Specifically, the primary endpoints were unlikely to be achieved as specified by the protocols (remission rate of 50% in the FMT arm vs. 25% in the placebo arm for Moayyedi and 70% vs. 23%, respectively, for Rossen). At the time of the interim analyses, only 15% and 8% of patients were in remission, respectively, in the trial by Moayyedi; no data was provided by Rossen et al.

Clinical remission

Clinical remission plus endoscopic response

The primary outcome in both trials was a composite of clinical remission plus an endoscopic response, which was defined using slightly different criteria (Moayyedi: full Mayo score <3 and complete healing of the mucosa at flexible sigmoidoscopy (i.e., endoscopic Mayo score = 0); Rossen: SCCAI score ≤2 and ≥1 point improvement from baseline on the combined Mayo endoscopic score of the sigmoid and rectum). The length of follow-up was also slightly different between the trials, with remission measured at 1.75 months (i.e., 7 weeks) and three months (i.e., 12 weeks), respectively.

Results from the individual studies varied. One trial (at low risk of bias) reported that significantly more patients in the FMT versus placebo (water retention enema) group achieved remission at 1.75 months (24% vs. 5%, RD 18% (95% CI 3%, 34%)) (Moayyedi) (Table 13). In contrast, the other trial (at moderately high risk of bias) reported no difference between FMT versus placebo (FMT using autologous feces) at three months (30% vs. 20%, RD 10% (95% CI -14%, 35%)) (Rossen). Despite one trial finding a significantly greater incidence of remission with FMT, both trials were terminated early as it was concluded that the primary endpoints were unlikely to be achieved as specified by the protocols.

Twelve month follow-up was provided by one trial (Moayyedi) for FMT group only; data for this extended follow-up was open-label. At this time, eight of the nine patients who were in remission at 1.75 months remained in remission without any relapse in their symptoms. Eleven patients randomized to FMT opted to continue this treatment for 1.5 to three months; of these patients, four were in remission at 12 months. Four patients elected to stop all their UC medications – mesalamine, long-term corticosteroids, both mesalamine and azathioprine, and infliximab (one patient each) – and remained remission free; three of these had been receiving FMT once a month, two electively and one as part of the trial that was discontinued.

Clinical remission

One trial (Rossen) (at moderately high risk of bias) also reported clinical remission alone, which was defined as a SCCAI score of up to 2; this outcome was a component of the composite primary outcome (above). As for the composite outcome, the authors found no differences between groups at 1.5 months (26% vs. 32%, RD -6% (95% CI -32%, 20%)) and three months (30% vs. 32%) (Table 13). The study reported that remission at 1.75 months but not at three months occurred in 0% of patients in the FMT group and 8% (n=2) patients in the placebo group; conversely, remission at three months (but not at 1.75 months) was achieved by 4% (n=1) versus 8% (n=2) patients, respectively.

Clinical response

Overall, no difference was seen between groups in clinical response, which was defined as a reduction in full Mayo clinic score by at least 3 points in one trial (Moayyedi) and as a decrease in SCCAI score at least 1.5 points in the other trial (Rossen) (Table 13).

Table 13. FMT vs. Placebo for Active Ulcerative Colitis: Clinical remission and response rates

Outcome	RCT	F/U	FMT* % (n/N)	Placebo* % (n/N)	RD (95% CI)†	p-value†
Clinical remission plus endoscopic response‡	Moayyedi 2015	1.75 mos.	24% (9/38)	5% (2/37)	18% (3%, 34%)	0.03
	Rossen 2015	3 mos.	30% (7/23)	20% (5/25)	10% (-14%, 35%)	0.41
	Moayyedi 2015	12 mos.	21% (8/38)	NR	NA	NA
Clinical remission§	Rossen 2015	1.5 mos.	26% (6/23)	32% (8/25)	-6% (-32%, 20%)	0.66
	Rossen 2015	3 mos.	30% (7/23)	32% (8/25)	-2% (-28%, 25%)	0.91
Clinical response**	Rossen 2015	1.5 mos.	44% (10/23)	52% (13/25)	-9% (-37%, 20%)	0.56
	Moayyedi 2015	1.75 mos.	39% (15/38)	24% (9/37)	15% (-6%, 36%)	0.16
	Rossen 2015††	3 mos.	48% (11/23)	52% (13/25)	-4% (-32%, 24%)	0.77

CI: confidence interval; F/U: follow-up; NA: not applicable; NR: not reported;RD: risk difference

* Treatment groups:
- Moayyedi: FMT vs. water (placebo) via retention enema.
- Rossen: FMT + bowel lavage using donor feces vs. autologous feces (placebo).

†Calculated

‡Clinical remission plus endoscopic response definitions:
- Moayyedi: full Mayo Clinic score <3 (range 0-12 (worst)) and complete healing of the mucosa during flexible sigmoidoscopy/ endoscopic Mayo Clinic score of 0
- Rossen 2015: SCCAI score ≤2 (range 0-19 (worst)) and ≥1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum (as compared with baseline sigmoidoscopy) 12 weeks after the first treatment.

§Defined as a SCCAI score ≤2. At 12 weeks, 0% (0/23) vs. 8% (2/25) in the FMT vs. control group were no longer in remission after being in remission at week 6 and 4% (1/23) vs. 8% (2/25), respectively, were in remission after not being in remission at week 6.

**Clinical response definitions:
- Moayyedi: reduction in full Mayo clinic score of ≥3 points (range 0-12 (worst)).
- Rossen 2015: reduction of ≥1.5 points on the SCCAI (range 0-19 (worst)).

††Between weeks 6 and 12, 4% (1/23) vs. 8% (2/25) in the FMT vs. control group lost clinical response and 9% (2/23) vs. 8% (2/25), respectively, gained clinical response.

Additional procedures

The moderately high risk of bias trial (Rossen) reported that through three months, the need for rescue therapy (not defined) for ongoing disease flare difference was similar between the FMT and placebo groups (22% vs. 12%, RD 10% (95% CI -11%, 31%)). Specifically, after the first FMT procedure, three patients in each group (FMT 13%, placebo 12%) required rescue therapy; after the second FMT procedure, an additional two patients (9%) in the FMT group required rescue therapy (per protocol).

In the low risk of bias trial (Moayyedi), the FMT group was followed for 12 months (during which treatment was open-label). Through this follow-up, one patient (3%) experienced a relapse of symptoms after taking a course of antibiotics and was treated with infliximab after declining additional FMT therapy; this patient continued to have symptoms.

Mortality
Mortality was not reported.

Other outcomes
Improvement in symptoms
Moayyedi et al.[90] (low risk of bias) evaluated UC symptom improvement using the Full Mayo score and found no statistically meaningful difference between groups in adjusted mean scores at 1.75 months (Table 14).

Quality of life
The same trial (Moayyedi 2015) (at low risk of bias) found no difference between groups in mean quality of life outcome measure scores at 1.75 months; both the Inflammatory Bowel Disease Questionnaire and the EuroQol-5 dimensions questionnaire were used to assess this outcome (Table 14).

Table 14. FMT vs. Placebo for Active Ulcerative Colitis: Symptom improvement and quality of life outcomes (Moayyedi 2015)

Outcome Measure	F/U	FMT* Mean ± SD	Placebo* Mean ± SD	MD (95% CI)†	p-value†
Full Mayo score (0-12 (worst))	1.75 mos.	6.1 (adj.)‡ (n=38)	6.3 (adj.)‡ (n=37)	NR	0.42
IBDQ score (0-224 (best))	1.75 mos.	152.1 (adj.)‡ (n=38)	149.4 (adj.)‡ (n=37)	NR	0.44
EQ-5D (0-100 (best))	1.75 mos.	68.5 (adj.)‡ (n=38)	70.1 (adj.)‡ (n=37)	NR	0.99

Adj.: adjusted; CI: confidence interval; EQ-5D: EuroQol 5 dimensions; F/U: follow-up; IBDQ: Inflammatory Bowel Disease Questionnaire; MD: mean difference; NR: not reported; SD: standard deviation

*Treatment groups: FMT vs. water (placebo) via retention enema

†As reported by the authors.

‡Adjusted for baseline values; standard deviations not reported. Full Mayo score and IBDQ had missing values which were replaced by their means. All analyses are intention-to-treat.

Effectiveness
No nonrandomized comparative (cohort) studies were identified that met the inclusion criteria.

4.1.2.2 FMT for IBD: Case Series

Because relatively few comparative studies have been published to date that report the comparative efficacy or effectiveness of FMT versus alternative treatments for IBD, case series with at least 70% follow-up and 30 patients (or 10 patients if in a pediatric population) were considered for inclusion in order to provide additional context on primary outcomes only.

Two prospective case series met these criteria, one of which evaluated the use of FMT in an adult Chinese population with moderate to severe Crohn's disease (with a mean duration of 7.4 years) (Cui 2015[36]) and the other evaluated the use of FMT in a pediatric population with mild to moderate ulcerative colitis (UC) (with a mean duration of 3.5 years) (Kunde 2013[73]). In the study evaluating the adult population, 41 patients (mean age 38 years, 37% female) underwent a single FMT (fresh or frozen stool) into the midgut via gastroscopy. In the pediatric population, FMT using fresh stool samples was

performed via retention enema on five consecutive days in 10 children (median age 18 (range, 7 to 20) years, 40% female). Additional study details are available in Appendix Table F7.

Clinical Remission
In the study evaluating adult patients with Crohn's disease, clinical remission (Harvey-Bradshaw Index (HBI) score ≤4 (range 0 to >18 (worst))) was attained in 70% of patients at three months and 60 of patients at six months (Cui).[36]

In the pediatric population with UC, 33% of patients achieved clinical remission (decrease in Pediatric UC Activity Index (PUCAI) score to <10 (range, 0-85 (worst)) through one month (Kunde).[73]

Clinical Improvement
In the study evaluating adult patients with Crohn's disease, clinical improvement (HBI decrease of >3 points) occurred 67% of patients at both three and six months (Cui).[36]

In the pediatric population with UC, the proportion of patients with clinical improvement (decrease of >15 points on the PUCAI) was 67% at one month (Kunde).[73]

Additional procedures
Additional procedures not reported.

Mortality
There were no IBS-related or all-cause deaths reported by either study, with one month (Kunde[73]) and six months (Cui [36]) of follow-up.

4.2 Key Question 2: Efficacy and Effectiveness of FMT according to route of administration, timing of administration, or type of preparation

Number of studies retained

Two RCTs and two nonrandomized comparative studies were identified that evaluate the impact of FMT in CDI patients. The results were stratified into separate sections that compare route of administration (1 RCT), timing of administration (1 cohort study), and type of fecal preparation (1 RCT, 1 cohort study). No studies of IBD patients were identified for this key question.

4.2.1 Clostridium difficile Infection (CDI)

4.2.1.1 Route of FMT Administration for Recurrent CDI

Studies included
One RCT (Youngster 2014)[142] compared colonoscopic to nasogastric (NG) tube fecal infusion in patients with recurrent CDI.

Efficacy
RCT characteristics
The trial was small, enrolling a total of 20 patients.[142] This single-center study was open-label, conducted in the US, and considered to be at moderately low risk of bias. Detailed patient and study characteristics are available in Table 15 as well as in Appendix Table F3.

Inclusion criteria and patient characteristics: Patients were eligible for inclusion based on the presence of recurrent or refractory CDI, which was defined as either: (a) recurrent CDI following three or more mild to moderate *C. difficile* infections and failure to respond to a six to eight week tapered course of vancomycin, or (b) two or more CDI episodes of such severity as to require hospitalization and cause considerable morbidity. CDI was diagnosed by the presence of diarrhea (≥3 watery stools each day) plus a positive toxin stool test. The median number of CDI recurrences at baseline was five (range, 2-16), and the median stool frequency was seven (range, 4-13) per day. The median time since the initial CDI diagnosis was lower in the colonoscopy versus the NG tube group (7 vs. 12 months). All but one patient (in the FMT group) had failed tapered vancomycin therapy; 12 patients (5/10 in colonoscopic and 7/10 in nasogastric groups) had previously received fidaxomicin therapy. Exclusion criteria included the inability to undergo FMT via either procedure, delayed gastric emptying syndrome, recurrent aspirations, significant immunodeficiency, allergies to foods present in the donor diet, or pregnancy.

Treatments: Patients were randomized to FMT via the colonoscopic (n=10) or the NG tube (n=10) route. Antibiotics were stopped 48 hours prior to infusion. In the colonoscopic group, patients underwent a standard bowel preparation prior to fecal delivery via endoscopy; patients were given loperamide to prevent loose stools during the procedure. In the NG tube group, patients received omeprazole for 48 hours before the infusion to decrease reflux; correct placement of the tube was verified via radiography prior to infusion. Both procedures utilized frozen donor feces (duration of storage ranged from 29 to 156 days). Donors had been screened for a number of pathogens, were between the ages of 18 and 50 years, and had a normal BMI; donors had no history of serious medical conditions and had not taken antibiotics in the six months prior. No additional co-interventions were reported.

Treatment failure protocol: Patients who did not respond to the initial FMT were offered a second FMT procedure using the administration route of their choice.

Risk of bias: The trial was found to be at moderately low risk of bias (Appendix Table E3). Methodological limitations included lack of blinded outcome assessment and failure to control for potentially confounding differences in baseline characteristics (specifically the time since initial diagnosis, as noted above). The trial was grant-funded.

Table 15. CDI RCTs comparing Colonoscopic to NG Tube FMT: Study and Patient Characteristics

	Youngster 2014	
	FMT: Colonoscopic Route (n=10)	FMT: Nasogastric Route (n= 10)
Patient demographics		
Females, %	60% (6/10)	50% (5/10)
Age, years; mean ± SD (range)	50.4 ± 28.8	58.6 ± 19.6
Recurrences of CDI; median (range)	4 (2-7)	5 (3-16)
Time since initial CDI; median (range)	7 (3-34) months	12 (3-66) months
History of CDI-related hospitalization, %	60% (6/10)	70% (7/10)
Stool frequency/ 24 hours; median (range)	6 (4-13)	7 (5-13)
Prior tapered vancomycin therapy, %	90% (9/10)	100% (10/10)
Prior fidaxomicin therapy, %	50% (5/10)	70% (7/10)
Hospital-acquired CDI, %	20% (2/10)	30% (3/10)

	Youngster 2014	
	FMT: Colonoscopic Route (n=10)	FMT: Nasogastric Route (n= 10)
Hospital inpatient at time of FMT, %	20% (2/10)	30% (3/10)
Self-reported health status 1 day pre-FMT (0-10 (best)); median (range)	5 (2-7)	4 (1-10)
Procedural characteristics		
Patient blinded to treatment received	No	
Antibiotics	Antibiotics not given as part of protocol; all antibiotics stopped 48 hours prior to FMT	
Bowel lavage?	Yes	No
Donor feces	Frozen (feces mixed with saline to volume of 90 cc and frozen; upon thawing was diluted further with saline to final volume of 250 cc (adults) or 160 (children)	Frozen (feces mixed with saline to volume of 90 cc and frozen); not further diluted upon thawing
Route of administration	Colonoscopic	NG tube
Repeat treatment	Second FMT via either route (patient choice) if no improvement, used feces from original donor	
Cross-over during study f/u period	20% (2/10)	0% (0/10)
Co-interventions	Loperamide (single dose, dose NR) at time of procedure	Omeprazole (2 mg/kg (up to 20 mg) per day) for 2 days prior to procedure
Length (%) f/u	2 months (100%), 6 months (mortality only) (100%)	
Country	US	
Funding	Grants (various)	
Risk of bias	Moderately Low	

CDI: *Clostridium difficile* infection; NG: nasogastric; NR: not reported

Efficacy Results

Cure

Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence through two months (i.e., 8 weeks). The presence of diarrhea was recorded via phone questionnaires given at predefined times during follow-up.

Cure following a single FMT procedure occurred similarly between the colonoscopy and NG administration routes (80% vs. 60%, RD 20% (95% CI -19%, 59%)) (Table 16);[142] the wide confidence intervals result from the very small sample size.

CDI recurrence details

All six patients who did not achieve cure had recurrence of CDI: one refused an additional FMT procedure (and no other treatment details were reported), and five chose to have a second FMT procedure (details in next section).[142]

Additional procedures:

If the initial procedure did not resolve CDI symptoms, patients were offered repeat FMT via the route of their choice. Five of the six patients who met these criteria underwent a second FMT procedure administered through an NG tube (2/10 vs. 3/10 for the colonoscopic vs. NG tube groups, respectively)

(Table 16). Cure without relapse through two months of these additional procedures was achieved in four of the five patients (2/2 vs. 2/3 for the colonoscopic vs. NG tube groups, respectively).[142]

Mortality:

Mortality attributed to CDI:

No deaths were attributed to CDI (Table 16).[142]

All-cause mortality:

Two patients died between two and six months.[142] The deaths were not reported according to treatment group. The first death occurred at 12 weeks in a patient who had had no CDI recurrences; the death was attributed to chronic obstructive pulmonary disease. The second death occurred at 21 weeks from laryngeal cancer that had metastasized.

Other outcomes

Symptoms: By two months post-FMT, the number of bowel movements was similar between the colonoscopic and NG tube groups (median 1 (IQR 1, 1) vs. median 2 (IQR 1, 2) p=0.165).[142]

Self-reported health status: At two months, the median patient-report health status was similar between colonoscopic and NG tube groups (median 5 (IQR 3, 6) vs. median 4 (IQR 2, 5), p=0.51).[142]

Table 16. CDI RCTs comparing Colonoscopic to NG Tube FMT: All outcomes

Study	Outcome	F/U	FMT: Colonoscopic Route	FMT: NG Tube Route	RD (95% CI)	p-value*
Youngster 2014	Cure† after single FMT, % (n/N)	2 mos.	80% (8/10)	60% (6/10)	20% (-19%, 59%)	0.34
	Second FMT procedure (all elected NG route), % (n/N)	≤2 mos.	20% (2/10)‡	30% (3/10)‡	-10% (-48%, 28%)	0.61
	Mortality attributed to CDI, % (n/N)	2 mos.	0% (0/10)	0% (0/10)	0%	1.0
	Mortality attributed to CDI, % (n/N)	6 mos.	0% (0/10)	0% (0/10)	0%	1.0
	All-cause mortality, % (n/N)	6 mos.	10% (2/20)		NA	NA
	Daily number of bowel movements, median (IQR)	2 mos.	1 (1-1)	2 (1-2)	NR	0.165
	Patient-reported health rating (1-10 (best)), median (IQR)	2 mos.	8 (7, 10)	7 (5, 8)	NR	0.51

CDI: *Clostridium difficile* infection; CI: confidence interval; F/U: follow-up; IQR: interquartile range; NA: not applicable; NG: nasogastric; NR: not reported; RD: risk difference

*Calculated.

†Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence

‡Cure without relapse following a second FMT (via NG tube) occurred in 100% (2/2) of patients who initially received FMT via colonoscopy and 66.7% (2/3) who initially received FMT via NG tube

4.2.1.2 Timing of FMT Administration for Recurrent CDI

Studies included

One retrospective database comparative study (Waye 2016)[136] compared FMT administration after two versus three or more CDI recurrences. No RCTs were identified that compared timing of administration.

Effectiveness

Nonrandomized comparative study characteristics

One retrospective comparative database study (Waye 2016)[136] met the inclusion criteria; the study was considered to be at moderately high risk of bias. Detailed information on patient and study characteristics are available in Appendix Table F4.

A review of the hospital's database was conducted and patients who underwent FMT for recurrent (≥2 recurrences of mild or moderate CDI, OR ≥1 recurrence of severe CDI) were included for analysis; recurrent CDI was defined as diarrhea (≥3 loose stools per day) plus a positive stool toxin test occurring in less than two months from the time the previous course of antibiotics was completed. The database included patients who had been treated since October 2012. Patients were divided into two groups based on the number of CDI recurrences at the time of FMT: 2 recurrences ("timely FMT") (n=30) versus ≥3 recurrences ("delayed FMT") (n=45). All patients received a standard course of vancomycin prior to FMT. FMT was conducted by colonoscopy or gastroscopy; both fresh (29%) and frozen (71%) stool were used and obtained from either universal donors (81%) or family members (19%). Patients who had recurrence of CDI following FMT were offered a second course of vancomycin followed by another FMT procedure. Patients had a mean age of 66 years, and 52% were female. The mean duration of disease was 30 weeks (95% CI 21, 39), and the mean number of CDI episodes was 4.0 (95% CI 3.7, 4.3): 3.0 versus 4.8 (95% CI 4.4, 5.1) for the timely versus delayed FMT groups, respectively. There were a number of potentially clinically meaningful differences in baseline characteristics between the timely versus delayed FMT groups, including the percentage of patients with a Charlson comorbidity index score of 0 to 2 (44% vs. 20%) or ≥3 (56% vs. 80%), number of CDI-related hospital admissions (mean 0.9 vs. 2.3), and mean number of days in the hospital for CDI (8.0 vs. 21.8). See Appendix Table G4 for additional details. The study was found to be at moderately high risk of bias due to a number of methodological limitations, including unblinded outcome assessment, lack of information regarding co-interventions, failure to control for confounding, and no information on whether there was differential follow-up between the groups (though complete follow-up was available in 94% of patients in the database) (Appendix Table E3). The study was conducted in Canada.

Effectiveness Results

Cure

Cure following a single FMT procedure was achieved similarly between the timely and delayed FMT groups (94% vs. 93%, p=0.93).[136] No other details were reported.

Other outcomes

No additional clinical effectiveness outcomes were reported.

Table 17. CDI Cohort Study comparing FMT after 2 versus ≥3 recurrences: All outcomes

Study	Outcome	F/U	"Timely FMT" (2 CDI recurrences), % (n/N)	"Delayed FMT" (≥3 CDI recurrences), % (n/N)	p-value*
Waye 2016	Cure† following single FMT	3 months	94% (28‡/30)	93% (42‡/45)	0.93

CDI: *Clostridium difficile* infection; F/U: follow-up
*Reported by the study.
†Cure was not clearly defined. The study did define recurrence of CDI as diarrhea (≥3 loose stools per day) plus a positive stool toxin test occurring in less than two months from the time the previous course of antibiotics was completed.
‡Numerators were back-calculated using the percentages and denominators provided.

4.2.1.3 Type of Feces Preparation used in FMT for Recurrent CDI

Studies included

One RCT (Lee 2016)[78] and one retrospective cohort study (Satokari 2015)[117] compared the impact of using frozen versus fresh feces for FMT in patients with recurrent CDI.

Efficacy

RCT characteristics

This non-inferiority trial enrolled a total of 232 patients and was conducted at six locations in Canada.[78] The trial was found to be at moderately low risk of bias. Detailed patient and study characteristics are available in Table 18 as well as in Appendix Table F5.

Inclusion criteria and patient characteristics: Adults with CDI (diarrhea (≤3 loose stools per day for 2 days) plus a positive *C. difficile* toxin test) that had recurred within eight weeks of appropriate antibiotic therapy were eligible for inclusion; patients with refractory CDI (i.e., did not respond to five days of vancomycin therapy (at 500 mg 4 times per day)) were also eligible. The mean number of recurrences was approximately 2.6, and the median duration of CDI was approximately 12 weeks. Exclusion criteria were neutropenia, high white blood counts, and toxic megacolon.

Treatments: Patients were randomized to infusion of either frozen (n=114) or fresh (n=118) feces, which was performed by retention enema. All antibiotics were terminated one to two days before the procedure. Feces were obtained from one of three donors. In the frozen feces group, the stool was frozen within five hours of collection and stored for up to 30 days; upon thawing the stool was used within 24 hours. In the fresh feces group, the stool was used within 24 hours of collection. Donors were negative for a number of pathogens, had not taken antibiotics in the previous three months, and had no history of serious medical conditions. No additional co-interventions were reported.

Treatment failure protocol: Those who did not show improvement within five to eight days of FMT were offered a second procedure using the same donor and preparation type as the first procedure; those who did not respond to the second infusion were offered either a third FMT or antibiotics.

Risk of bias: The trial was considered to be at moderately low risk of bias (Appendix Table E3). Methodological limitations included failure to adhere to the intention to treat principle (because 6 randomized patients were excluded from analysis post-randomization) and failure to control for potentially confounding differences in baseline characteristics (including inpatient status, mild CDI, severe CDI). The trial was grant-funded.

Table 18. CDI RCTs comparing Frozen versus Fresh Feces for FMT: Study and Patient Characteristics

	Lee 2016	
	FMT: Frozen Feces (n=108*)	FMT: Fresh Feces (n=111*)
Patient demographics		
Females, %	66.7% (72/108)	66.7% (74/111)
Age, years; mean ± SD (range)	73.0 ± 16.4	72.5 ± 16.2
Recurrences of CDI; mean ± SD	2.7 ± 1.7	2.5 ± 1.5
<2 recurrences of CDI, %	92.6% (100/108)	84.7% (94/111)
≥2 recurrences of CDI, %	7.4% (8/108)	15.3% (17/111)
Recurrent CDI, %	94.4% (102/108)	92.0% (102/111)
Refractory CDI, %	5.6% (6/108)	8.1% (9/111)
Time since initial CDI; median (range)	91 (18-842) days	82 (6-1351) days
Mild CDI†, %	38.0% (41/108)	29.7% (33/111)
Moderate CDI†, %	45.4% (49/108)	46.0% (51/111)
Severe CDI†, %	16.7% (18/108)	24.3% (27/111)
Inpatient at time of FMT, %	47.4% (51/107)	54.1% (60/111)
Stool frequency/ 24 hours	NR	NR
Abdominal pain, %	58.3% (63/108)	63.3% (69/109)
Fever, %	32.4% (35/108)	32.4% (36/111)
Days of antibiotic use prior to FMT, median (range)	58 (13-645)	43.5 (6-811)
Prior tapered vancomycin therapy, %	94.3% (100/106)	90.0% (97/109)
Vancomycin + metronidazole pre-FMT, %	34.3% (37/108)	32.7% (35/107)
Healthcare-acquired CDI, %	47.7% (51/107)	54.1% (60/111)
Community-acquired CDI, %	52.3% (56/107)	45.9% (51/111)
Procedural characteristics		
Patient blinded to treatment received	Yes	
Antibiotics	Yes (discontinued 1-2 days pre-FMT)	
Bowel lavage?	No	No
Donor feces	Frozen (100g fresh donor feces (≤5 hours of collection) mixed with water to volume of 300 ml and strained and frozen at -20°C for ≤30 days); 50 ml was used for FMT ≤24 hours of thawing. Three donors were used for the study.	Fresh (100g fresh donor feces (≤5 hours of collection) mixed with water to volume of 300 ml and strained; 50 ml was used for FMT ≤24 hours. Three donors were used for the study.
Route of administration	Retention enema	Retention enema
Repeat treatment	Second FMT (same donor and prep) if no improvement; if no improvement after 2 FMTs, a third FMT or antibiotics were offered	
Cross-over during study f/u period	0% (0/108)	0% (0/111)
Co-interventions	NR	NR
Length (%) f/u	13 weeks (91%)	
Country	Canada	
Funding	Grants (various); authors disclosed a number of financial relationships with industry‡	
Risk of bias	Moderately Low	

CDI: *C. difficile* infection; f/u: follow-up; NR: not reported; SD: standard deviation

*Patient demographics reported after 13 patients excluded or withdrew post-randomization but pre-FMT (in the frozen feces group, 4 withdrew and 2 were excluded "for safety reasons"; in the fresh feces group, 3 withdrew and 4 were excluded "for safety reasons")
†Severity of CDI based on temperature, white blood cell count, and serum creatinine level at baseline
‡Dr. Lee reports participating in clinical trials for ViroPharma, Actelion, Cubist, and Merck and serving as a member of the advisory boards for Rebiotix and Merck. Dr. Steiner reports receiving consulting fees and an unrestricted grant from Cubist, consulting fees and a phase 3 trial contract from Merck Canada, and a phase 3 trial contract from Sanofi Pasteur; additionally, his institution was recently approved as a site for a phase 2b randomized clinical trial of frozen stool product with Rebiotix. Dr Petrof reports holding a patent for synthetic stool formation. Dr Crowther reports receiving grants from the Heart and Stroke Foundation of Ontario, Leo Pharma, and Bayer, as well as funding for educational materials from Alexion, Ortho Clinical Diagnostics, BMS-Pfizer Alliance, Leo Pharma, Bayer, Celgene, Shire, and CSL Behring. Dr Kim reports serving as a member of the advisory board for Rebiotix.

Efficacy Results

Cure

Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence through 3.25 months (i.e., 13 weeks), and occurred similarly between the frozen versus fresh feces groups after a single procedure (52.8% vs. 50.5%, RD 2.3% (95% CI -10.9%, 15.6%) (Table 19); there were also no differences between groups in cure rate after multiple FMT procedures (Table 19).[78]

The trial also reported cure results according to a per-protocol analysis, from which patients who received CDI antibiotic treatment during the study period or who received both fresh and frozen fecal infusions (i.e., cross-over patients) were excluded. In this analysis, cure rates within 13 weeks were similar between groups regardless of the number of procedures (1 FMT: 63% (57/91) vs. 62% (54/87); all FMTs: 96% (87/91) vs. 97% (84/87)).

The study concluded that frozen feces was noninferior to fresh feces for FMT infusion in this population.

Table 19. CDI RCTs comparing Colonoscopic to NG Tube FMT: All outcomes (Lee 2016)

RCT	F/U	Outcome	FMT: Frozen Feces	FMT: Fresh Feces	RD (95% CI)	p-value*
Lee 2016	3.25 mos. from last FMT	Cure† after 1 FMT, % (n/N)	52.8% (57/108)	50.5% (56/111)	2.3% (-10.9%, 15.6%)	0.73
		Cure† after ≤2 FMTs, % (n/N)	75.0% (81/108)	70.3% (78/111)	4.7% (-7.1%, 16.5%)	0.43
		Cure† after ≤5 FMTs, % (n/N)	87.0% (94/108)	81.1% (90/111)	6.0% (-3.7%, 15.6%)	0.23
		Cure† after all FMTs, % (n/N)	90.7% (98/108)	85.6% (95/111)	5.2% (-3.4%, 13.7%)	0.24
		Mortality attributed to CDI, % (n/N)	1.9% (2/108)	1.8% (2/111)	0.1% (-3.5%, 3.6%)	0.98
		All-cause mortality, % (n/N)	5.6% (6/108)	11.7% (13/111)	-6.2% (-13.5%, 1.2%)	0.11

CI: confidence interval; F/U: follow-up; NG: nasogastric; RD: risk difference
*Calculated.
†Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence

Additional procedures:
The percentage of patents in each group who underwent additional FMT procedure(s) was not clearly reported. The total number of procedures per patient ranged from one to 13.[78] Ultimately, after anywhere from two to 13 procedures, 41 patients in the frozen feces group and 39 patients in the fresh feces group achieved cure through 3.25 months.

Mortality:
Mortality attributed to CDI:
There was no difference between the frozen and fresh feces groups in the incidence of CDI-related mortality (1.9% vs. 1.8%)[78] (Table 19).

Two deaths were attributed to CDI in each group and occurred between six and 10 days from the last FMT procedure. In the frozen feces group, one 100-year old patient with chronic renal failure and unresolved CDI died 7 days post-FMT; one 84-year old patient died 10 days post-FMT. In the fresh feces group, one 65-year old patient with hypercarbic respiratory failure died 6 days after the last FMT, and one 88-year old patient died 7 days post-FMT.

All-cause mortality:
The incidence of death from any cause was slightly lower in the frozen feces group but the difference did not reach statistical significance (5.6% vs. 11.7%, RD -6.2% (95% CI -13.5%, 1.2%)) (Table 19).[78]

Aside from the four deaths attributed to CDI (see above), there were a total of 15 deaths from other causes.[78] Deaths occurred between three and 83 days from the last FMT procedure (median, 29 days); the median time to death from the last infusion was 16.5 days in the fresh feces group and 31 days in the frozen feces group. Death was caused by cardiac arrest, cardiac ischemia, congestive heart failure, ischemic stroke, respiratory failure, gastrointestinal bleeding, sepsis, pneumonia, and/or pyelonephritis. These patients ranged in age from 59 to 95 years (median, 85 years).

Other outcomes
No other outcomes were reported.

Effectiveness
Nonrandomized comparative study characteristics
One retrospective cohort study (Satokari 2015)[117] met the inclusion criteria; the study was considered to be at moderately high risk of bias. Detailed information on patient and study characteristics are available in Appendix Table F5.

All recurrent CDI patients treated with FMT between December 2007 and February 2014 at a single hospital in Finland were included. CDI was diagnosed by a culture and toxin test, and all patients had failed standard antibiotic therapy (details not reported). The mean number of CDI recurrences was 4.3 (range, 1-12), and the mean time from the first CDI was 147 days (range, 42-360). Patients underwent bowel lavage followed by colonoscopic infusion of either frozen (n=23) or fresh (n=26) feces from universal donors, volunteers, or relatives. All patients were given vancomycin, which was terminated approximately 36 hours pre-FMT. Patients with post-FMT recurrence were treated on an individual basis (i.e., no specific protocol was followed). Compared with the frozen group, those who received fresh feces were slightly younger (mean age 61 vs. 52 years), less likely to be female (61% vs. 77%), and had had slightly more CDI recurrences (mean 4.6 vs. 4.0). The study was considered to be at moderately high risk of bias due to the following methodological limitations: lack of blind outcome assessment and failure to control for potentially confounding differences between groups (Appendix Table E2). Complete follow-up through 12 weeks was available for 100% of patients. Outcomes were also reported through one year with follow-up of 86% of patients, however there was differential follow-up between the frozen versus fresh feces groups (74% vs. 96%).

Effectiveness Results

Cure
Completed resolution of symptoms following a single procedure occurred similarly between the frozen and fresh groups through the first three months (96% vs. 96%) as well as between four and 12 months (88% vs. 88%) (Table 20).[117]

Of the two patients who did not achieve cure through three months, one (in frozen group) underwent a successful repeat FMT and the other (in fresh group) received additional vancomycin but died at two months. For those followed for one year, four patients (two in each group) had CDI recurrences; all had achieved cure through three months. In the frozen group, both were treated with vancomycin, one of which ultimately died from CDI-related complications. In the fresh group, recurrence was treated with FMT in one patient and with intravenous immunoglobulins in the other (treatment outcomes not reported).

Additional procedures
Through three months, one patient in the frozen group underwent a second FMT procedure (4% vs. 0% for frozen vs. fresh, p=0.29) (Table 20), which successfully treated the CDI.[117]

Between four and 12 months, one patient in the fresh group underwent a second infusion; the outcome of which was not reported (0% vs. 4% for frozen vs. fresh, p=0.41) (Table 20).[117]

Mortality:

Mortality attributed to CDI:

In the first three months, one patient in the fresh feces group died at two months; the death was attributed to multiple causes including CDI; the patient had CDI recurrence which was unsuccessfully treated with vancomycin. The patient had other health problems (was on chronic dialysis and had atherosclerosis) that may have attributed to her death. The incidence of CDI-related mortality was similar between the frozen and fresh groups (0% vs. 4%, p=0.35) (Table 20).[117]

Between four and 12 months, one patient in the frozen group died from CDI; the patient had experienced complete symptom resolution during the first three months but later had a recurrence, which was unsuccessfully treated with antibiotics (details not reported). During this time period, deaths attributed to CDI occurred similarly between the frozen and fresh groups (6% vs. 0%, p=0.23) (Table 20).[117]

All-cause mortality:

Through three months, all-cause death occurred similarly between the frozen and fresh feces groups (0% vs. 4%, p=0.35) (Table 20); the one death that occurred (in the fresh group) was attributed to CDI.[117]

The incidence of all-cause mortality between four and 12 months was also statistically similar between groups (12% vs. 4%, p=0.34) (Table 20). Two deaths occurred in the frozen group (12% (2/17)), one of which was CDI-related, and the other was due to arterial thrombosis (although the patient had had a recurrence of CDI and was treated with vancomycin). One death was reported for the fresh group for this time period (4% (1/25)), the cause of which was not related to CDI but not further specified.[117]

Other outcomes

No additional clinical effectiveness outcomes were reported.

Table 20. CDI Cohort Study comparing Frozen to Fresh Feces for FMT: All outcomes

Study	F/U	Outcome	FMT: Frozen Feces, % (n/N)	FMT: Fresh Feces, % (n/N)	p-value*
Satokari 2014	≤3 months	Complete resolution of symptoms	96% (22/23)	96% (25/26)	0.93
		Additional FMT procedure	4% (1/23)	0% (0/26)	0.29
		Mortality attributed to CDI	0% (0/23)	4% (1/26)†	0.35
		All-cause mortality	0% (0/23)	4% (1/26)†	0.35
	4-12 months	Complete resolution of symptoms	88% (15/17)	88% (22/25)	0.98
		Additional FMT procedure	0% (0/17)	4% (1/25)	0.41
		Mortality attributed to CDI	6% (1/17)‡	0% (0/25)	0.23
		All-cause mortality	12% (2/17)§	4% (1/25)**	0.34

CI: confidence interval; F/U: follow-up; RD: risk difference

*Calculated.

†Nonresponder who had universal atherosclerosis and was on chronic dialysis; patient treated with vancomycin for recurrence of CDI and died of multiple medical problems two months after FMT.

‡Patient developed recurrent CDI, was subsequently treated with antibiotics, but died from CDI.

§One patient had mortality attributed to CDI (see ‡); the other patient developed recurrent CDI, was treated with antibiotics (treatment outcome NR), and ultimately died of arterial thrombosis.

**Death unrelated to CDI; cause NR.

4.3 Key Question 3: Safety

Number of studies retained

All included comparative studies and non-comparative were evaluated for harms and complications.

4.3.1 Clostridium difficile Infection (CDI)

4.3.1.1 FMT vs. Antibiotics for recurrent CDI

Two RCTs (Cammarota 2015[25], van Nood 2013[131]) and one prospective cohort study (Lagier 2015[74]) compared FMT to antibiotics in patients with recurrent CDI; all reported on adverse events.

RCTs

Serious adverse events: No serious adverse events (including procedure-related death) occurred in either group[25,131]).

Non-serious adverse events: On the day of the FMT procedure, the following non-serious adverse events were reported to occur in the FMT group (in decreasing order of frequency) (Table 21): diarrhea (94 - 95%)[25,131], bloating (60%)[25], abdominal pain or cramps (31 - 60%)[25,131], belching (19%)[131], nausea (6%)[131], and dizziness with diarrhea (6%; the patient had known autonomic dysfunction)[131]. One trial[131] reported no cases of vomiting, constipation, or infection in the FMT group (0/16) on the day of the procedure. No adverse events were reported to occur on the day of the bowel lavage procedure in the control group (n=13) in the van Nood trial.[131]

Through 2.5 months follow-up, one trial[131] reported the following non-serious adverse events to occur statistically similarly between FMT and vancomycin groups (Table 21): constipation (19% vs. 12%), infection (13% vs. 4%), gastrointestinal complaints (0% vs. 8%), indigestion (0% vs. 4%), and nausea (0% vs. 4%). In addition, there were no cases in either treatment group of belching, vomiting, abdominal cramps, abdominal pain, or diarrhea. The other trial reported no vancomycin-attributed adverse events occurred.[25]

Table 21. FMT vs. Vancomycin alone vs. Vancomycin + bowel lavage for recurrent CDI: Adverse events in RCTs

Outcome	Study	FMT + bowel lavage % (n/N)	Vancomycin + bowel lavage % (n/N)	RD (95% CI)* RR (95% CI)*	p-value*
Serious AEs occurring on day of procedure†					
Death	Van Nood 2013	0% (0/16)	NR	NC	NC
	Cammarota 2015	0% (0/20)	NR	NC	NC
Non-serious AEs occurring on day of procedure†					
Diarrhea	Van Nood 2013	94% (15/16)	NR	NC	NC
	Cammarota 2015	95% (19/20)	NA	NC	NC
Abdominal cramps	Van Nood 2013	31% (5/16)	NR	NC	NC
	Cammarota 2015	60% (12/20)	NR	NC	NC
Bloating	Cammarota 2015	60% (12/20)	NR	NC	NC
Abdominal pain	Van Nood 2013	13% (2/16)	NR	NC	NC

Outcome	Study	FMT + bowel lavage % (n/N)	Vancomycin + bowel lavage % (n/N)	RD (95% CI)* RR (95% CI)*	p-value*
Belching	Van Nood 2013	19% (3/16)	NR	NC	NC
Nausea	Van Nood 2013	6% (1/16)	NR	NC	NC
Dizziness with diarrhea‡	Van Nood 2013	6% (1/16)‡	NR	NC	NC
Vomiting	Van Nood 2013	0% (0/16)	NR	NC	NC
Constipation	Van Nood 2013	0% (0/16)	NR	NC	NC
Infection	Van Nood 2013	0% (0/16)	NR	NC	NC
Non-serious AEs occurring through 2.5 months					
Constipation	Van Nood 2013	19% (3/16)	12% (3/26)§	RD 7% (-16%, 30%) RR 1.63 (0.37, 7.10)	0.52
Infection	Van Nood 2013	13% (2/16)**	4% (1/26)§	RD 9% (-9%, 26%) RR 3.25 (0.32, 33.01)	0.30
Gastrointestinal complaints	Van Nood 2013	0% (0/16)	8% (2/26)§	RD -8% (-18%, 3%) RR 0.0 (NC)	0.26
Indigestion	Van Nood 2013	0% (0/16)	4% (1/26)§	RD -4% (-11%, 4%) RR 0.0 (NC)	0.43
Nausea	Van Nood 2013	0% (0/16)	4% (1/26)§	RD -4% (-11%, 4%) RR 0.0 (NC)	0.43
Belching	Van Nood 2013	0% (0/16)	0% (0/26)	RD 0%	1.0
Vomiting	Van Nood 2013	0% (0/16)	0% (0/26)	RD 0%	1.0
Abdominal cramps	Van Nood 2013	0% (0/16)	0% (0/26)	RD 0%	1.0
Diarrhea	Van Nood 2013	0% (0/16)	0% (0/26)	RD 0%	1.0
Abdominal pain	Van Nood 2013	0% (0/16)	0% (0/26)	RD 0%	1.0
Hospital admission (for choledocholithiasis)	Van Nood 2013	6% (1/16)††	0% (0/26)	RD 6% (NC) RR NC	1.0

AE: adverse event; CI: confidence interval; F/U: follow-up; MD: mean difference NA: not applicable; NC: not calculable; NR: not reported; RD: risk difference; RR: risk ratio; VAS: Visual Analog Scale

*Calculated

†For van Nood, complications on day of procedure occurred within 3 hours of FMT

‡Patient had autonomic dysfunction

§Complications were pooled between the vancomycin-alone (n=13) and vancomycin + bowel lavage (n=13) groups. Details on which group the event(s) occurred in are as follows:

- Nausea: vancomycin group (n=1)
- Constipation: vancomycin group (n=1), vancomycin + bowel lavage group (n=2)
- Gastrointestinal complaints: vancomycin + bowel lavage group (n=2), consisting of excess gas in one patient, persistent diarrhea in other patient (who was later diagnosed with celiac disease)
- Infection: vancomycin + bowel lavage group (n=1), which was urinary tract infection (antibiotics prescribed)
- Other adverse events: vancomycin group (n=1), which was increased pain due to rheumatoid arthritis (analgesics prescribed)

**Infections: urinary tract infection in one patient (patient had history of recurrent such infections, antibiotics prescribed), fever during hemodialysis (antibiotics prescribed)

††Hospitalization on day 56 for symptomatic choledocholithiasis; endoscopic retrograde cholangiopancreatography performed and stone removed

Cohort studies
Adverse events were reported by the single cohort study[74] that compared early FMT (i.e., first CDI episode) (n=16) to "non-early transplantation", which was antibiotics in 42 patients that had up to two CDI relapses and FMT in 3 patients who had more than three CDI relapses. Adverse events were reported for the 33 FMT procedures only.

Serious adverse events: One patient (3% (1/3) transplantations) experienced an acute cardiac insufficiency on the days of the FMT procedure; no other details were reported, and the study described this as a minor event.

Non-serious adverse events: On the day of the procedure, 73% FMT recipients experienced diarrhea (24/33 transplantations), which resolved by the following day. One patient had considerable nausea from the NG tube (3% (1/33) transplantations), and one patient refused insertion of the NG tube (3% (1/33) transplantations).

4.3.1.2 Route of FMT Administration for recurrent CDI

RCTs
One trial[142] of 20 patients that compared route of fecal administration (colonoscopic vs. nasogastric tube) reported on adverse events, although events were not stratified by treatment group. Patients were followed through two months for all outcomes and through six months for mortality only.

Serious adverse events: No serious adverse events (including death) were attributed to FMT.

Non-serious adverse events: Mild abdominal discomfort and bloating attributed to FMT occurred in 20% (4/20) of patients. Fever two days post-FMT was reported in one pediatric patient (5%), which resolved on its own.[142]

4.3.1.3 Timing of FMT Administration for Recurrent CDI

The retrospective database study (Waye 2016)[136] that compared FMT administration after two versus three or more CDI recurrences did not report on adverse events.

4.3.1.4 Type of Feces Preparation used in FMT for Recurrent CDI

One RCT (Lee 2016, N=232)[78] and one retrospective cohort study (Satokari 2015, N=49)[117] compared the impact of using frozen versus fresh feces for FMT in patients with recurrent CDI; both reported adverse events.

RCTs
Serious adverse events: No serious adverse events (including death) were attributed to FMT; patients were followed for 3.25 months.[78]

Non-serious adverse events: In the first 24 hours after FMT, the following mild to moderate symptoms were reported to occur similarly across both groups (data were not stratified by group, and patient numbers not reported): transient diarrhea (70%), abdominal cramps (10%), and nausea (<5%). Through 3.25 months follow-up, the following were reported but considered to be unrelated to FMT: excess flatulence (25%), constipation (20%), urinary tract infection (<5%), respiratory tract infection (<1%), blood in stool (<1%), and exacerbation of pre-existing rheumatoid arthritis after immunosuppressants were stopped. In addition, hospitalization for illnesses unrelated to FMT occurred similarly between the

frozen and fresh feces groups (7.4% (8/108) vs. 3.6% (4/111), RD 3.8% (95% CI -2.2%, 9.8%)) through 13 weeks.[78]

Cohort studies

Serious adverse events: No serious adverse events were attributed to FMT through 12 months, including transmittal of infections from the donated feces.[117]

Non-serious adverse events: Adverse events were reported through 12 months. A mild short-term fever occurred in two patients in the frozen FMT group and in no patients in the fresh FMT group; this difference was not statistically significant (12% (2/17) vs. 0% (0/25), p=0.083) and no other details were reported.[117]

4.3.1.5 FMT for recurrent CDI

Of the 13 case series included that assessed FMT for the treatment of CDI, 12 reported on adverse events, two of which were exclusively in pediatric patients.[4,21,51,63,67,70,72,77,85,98,100,111,112] Adverse events are presented in table format in Appendix G6.

Serious adverse events: Eight case series[4,21,67,77,85,98,100,111] (total N=607) reported on FMT-related mortality; across these studies, there was one instance of death attributed to FMT (1% (1/80)).[67] This patient had advanced esophageal cancer and cachexia, aspirated during sedation for the FMT procedure, and died the next day from respiratory failure. There was one instance of a microperforation caused by a periprocedural biopsy in a region of the small bowel believed to have ischemic injury; the patient had a history of a subtotal colectomy as well as chronic dilation of the small bowel and recovered from the microperforation with conservative treatment.[100] One case series reported that another patient (1% (1/80)) required hospitalization for abdominal pain attributed to FMT, though the pain was self-limited.[67] Another study noted that 4.1% (6/146) patients were hospitalized for diarrhea attributed to either FMT or CDI.[4] Three case series[77,85,98] (total N=198) made statements indicating that no serious adverse events occurred.

Non-serious adverse events: The following non-serious adverse events were reported (in decreasing order of frequency): transient constipation with excess flatulence (10% (9/94))[77], diarrhea in CDI-negative patients (4.8% (7/146))[4], diarrhea (4% (3/80))[67], bloating and abdominal discomfort (4% (3/80))[67], constipation in CDI-negative patients (2.7% (4/146))[4], minor mucosal tear during procedure (1% (1/80))[67], fever (1% (1/80))[67], and nausea (1% (1/80))[67]. Three case series[51,63,111] (total N=147) made statements indicating that no adverse events occurred. One case series[98] indicated that 82% of patients (28/34) experienced at least one adverse event through six months (though not all were attributed to the procedure), including gastrointestinal disorders, infections, general malaise (chills, fever, etc.), respiratory disorders, musculoskeletal disorders, nervous system disorders, etc.)

In case series of pediatric patients, the following non-serious adverse events were reported (in decreasing order of frequency): short-term gastrointestinal distress (60% (6/10))[112], mucoid stools (20% (2/20) across two studies (10% in each)),[72,112], and vomiting (10% (1/10)).[72]

Additional adverse events that appeared to be unrelated to FMT included hospitalization (8% (6/80))[67], IBD flare requiring hospitalization (1% (3/80))[67], Crohn's Disease flare (1% (1/80))[67], hip pain (1% (1/80))[67], and pertussis (1% (1/80))[67].

4.3.2 Inflammatory Bowel Disease (IBD)

4.3.2.1 FMT vs. Placebo for IBD (UC)

Two RCTs (Moayyedi 2015[90], Rossen 2015[109]) compared FMT to placebo in patients with ulcerative colitis (UC); both reported on adverse events.

RCTs

Serious adverse events: Overall, there were no differences between groups in the occurrence of any serious adverse event in either trial (8% (5/61) vs. 6% (4/62), pooled RD 2% (95% CI -7%, 11%).[90,109]

Moayyedi et al. (low risk of bias) reported an overall incidence of serious adverse events of 8% in the FMT group versus 5% in the placebo group over 1.75 months of follow-up (RD 3% (95% CI -9%, 14%) (Moayyedi 2015[90]); events included worsening colitis requiring urgent colectomy (0% vs. 3%, respectively), diagnosis change to Crohn's disease requiring antibiotic treatment (5% vs. 3%), and *C. difficile* positive after completion of therapy (3% vs. 0%). It is unclear if any of these events were directly related to FMT treatment. Additionally, this study reported 12-month outcomes for patients in the FMT group, during which time another FMT patient required a colectomy for failure of UC medical therapy.

Rossen et al. (moderately high risk of bias) observed two serious adverse events in both the FMT and placebo groups through three months (9% vs. 8%, RD 1% (95% CI -15%, 16%).[109] Adverse event details were largely not reported by treatment group and included severe small bowel Crohn's disease (treated with antibiotics), severe illness from primo cytomegalovirus infection (placebo group), abdominal pain (recovered spontaneously), and surgery for cervical carcinoma.

Non-serious adverse events: Mild procedural-related adverse events were reported by one trial (moderately high risk of bias); most events were transient and disappeared spontaneously within 2 days.[109] Overall, no significant difference was noted between the FMT group (donor feces) and the placebo group (FMT using autologous feces) in the occurrence of any mild adverse event (78% vs. 64%, RD 14% (95% CI -11%, 40%) All mild adverse are listed in Table 22; the only adverse events that occurred differentially between groups were increased stool frequency/diarrhea, which was more common with donor FMT (30% vs. 4%, RD 26% (95% CI 6%, 47%), and abdominal cramps, which was less common with donor FMT (0% vs. 24%; RD -24%, 95% CI -41%, -7%).

Table 22. FMT vs. Placebo for Ulcerative Colitis: Adverse events

Outcome	Study*	F/U	FMT % (n/N)	Placebo % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Serious adverse events						
Diagnosis of Crohn's colitis§	Moayyedi 2015	1.75 mos.	5% (2/38)	3% (1/37)	RD 3% (-6%, 11%) RR 1.9 (0.2, 20.6)	0.57
Worsening colitis requiring urgent colectomy	Moayyedi 2015	0.75 mos.	0% (0/38)	3% (1/37)	RD -3% (-8%, 3%) RR NC	0.31
C. difficile positive at end of therapy	Moayyedi 2015	1.75 mos.	3% (1/38)	0% (0/37)	RD 3% (NC) RR NC	0.32
Any "serious" adverse event	Moayyedi 2015	1.75 mos.	8% (3/38) *(sum of above)*	5% (2/37) *(sum of above)*	RD 3% (-9%, 14%) RR 1.5 (0.3, 8.2)	0.67
	Rossen	3 mos.	9% (2/23)	8% (2/25)	RD 1% (-15%, 16%)	0.93

Outcome	Study*	F/U	FMT % (n/N)	Placebo % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
	2015‡				RR 1.1 (0.2, 7.1)	
Mild AEs occurring on day of procedure						
Abdominal murmurs	Rossen 2015	Peri-proc.	17% (4/23)	32% (8/25)	RD -14% (-39%, 9%) RR 0.54 (0.2, 1.6)	0.25
Increase of stool frequency/diarrhea	Rossen 2015	Peri-proc.	30% (7/23)**	4% (1/25)	RD 26% (6%, 47%) RR 7.6 (1.0, 57.2)	0.02
Abdominal cramps	Rossen 2015	Peri-proc.	0% (0/23)	24% (6/25)	RD -24% (-41%, -7%) RR NC	0.01
Abdominal pain	Rossen 2015	Peri-proc.	4% (1/23)	16% (4/25)	RD -12% (-28%, 5%) RR 0.27 (0.03, 2.3)	0.19
Nausea	Rossen 2015	Peri-proc.	9% (2/23)	4% (1/25)	RD 5% (-9%, 19%) RR 2.2 (0.21, 22.4)	0.51
Fever	Rossen 2015	Peri-proc.	9% (2/23)	0% (0/25)	RD 9% (NC) RR NC	0.14
Vomited fecal infusion due to malposition of tube	Rossen 2015	Peri-proc.	9% (2/23)	0% (0/25)	RD 9% (NC) RR NC	0.14
Discomfort during tube placement	Rossen 2015	Peri-proc.	4% (1/23)	4% (1/25)	RD 0.4% (-11%, 12%	0.95
Headache	Rossen 2015	Peri-proc.	4% (1/23)	4% (1/25)	RD 0.4% (-11%, 12%	0.95
Vomited bowel preparation after replacement of ND tube before FMT start	Rossen 2015	Peri-proc.	4% (1/23)	0% (0/25)	RD 4% (NC) RR NC	0.30
Vomiting	Rossen 2015	Peri-proc.	4% (1/23)	0% (0/25)	RD 4% (NC) RR NC	0.30
Mild constipation	Rossen 2015	Peri-proc.	4% (1/23)	0% (0/25)	RD 4% (NC) RR NC	0.30
Dizziness	Rossen 2015	Peri-proc.	0% (0/23)	4% (1/25)	RD -4% (-12%, 4%) RR NC	0.34
Malaise	Rossen 2015	Peri-proc.	0% (0/23)	4% (1/25)	RD -4% (-12%, 4%) RR NC	0.34
Infectious complications	Rossen 2015	Peri-proc.	0% (0/23)	0% (0/25)	NC	1.0
Any mild adverse event††	Rossen 2015	Peri-proc.	78% (18/23) *(total of above)*	64% (16/25) *(total of above)*	RD 14% (-11%, 40%) RR 1.2 (0.8, 1.8)	0.28
Mild AEs reported through 3 months						
Traveler's diarrhea requiring antibiotics	Rossen 2015	3 mos.	4% (1/23)	0% (0/25)	RD 4% (NC) RR NC	0.30

AE: adverse event; F/U: follow-up; NC: not calculable; ND: nasoduodenal; Peri-op: peri-operatively; RD: risk difference; RR: risk ratio

* Treatment groups:

- Moayyedi: FMT vs. water (placebo) via retention enema.

- Rossen: FMT + bowel lavage using donor feces vs. autologous feces (placebo).

†Calculated

‡Events were not reported by group: consisted of severe small bowel Crohn's disease treated with antibiotics at 5 weeks, severe illness from primo cytomegalovirus infection 7 weeks after first infusion (not related to treatment, patient was in placebo group), abdominal pain 11 weeks after treatment (recovered spontaneously), and operation for cervix carcinoma 6 weeks after first treatment (not related to treatment).

§Developed patchy inflammation of colon and rectal abscess formation; symptoms resolved with antibiotic treatment.

**Reporting is inconsistent for this adverse event: listed as 30.4% (7/23) in text, but 21.7% (5/23) in Supplementary Table 1; results are reported as indicated in text.

††Most mild adverse events were transient and disappeared spontaneously within 2 days, including fever (p = 0.28 between groups). Patients could have more than one event, see list that precedes.

4.3.2.2 FMT for IBD

Two prospective case series evaluated FMT for the treatment of IBD, both of which reported on adverse events. One evaluated FMT for treatment of refractory Crohn's disease in adult Chinese patients (Cui 2015[36]) and the other evaluated a pediatric population with mild to moderate UC treated with FMT given on each of five consecutive days (Kunde 2013[73]). Adverse events are presented in table format in Appendix G6.

Serious adverse events: Cui et al. reported no serious adverse events through 15 months.[36] Kunde et al. reported one serious adverse event (10%); the child developed disabling hematochezia three weeks post-FMT and was treated with corticosteroid enema therapy; the event was attributed to a UC flare and unrelated to FMT.[73]

Non-serious adverse events: Cui et al. found that 23% (7/30) of patients experienced increased diarrhea and 7% (2/30) had a fever within six hours post-procedure; no instances of pain or fecal ileus were reported through 15 months follow-up.[36]

In the case series of 10 pediatric patients, the following non-serious adverse events were reported through one month: bloating/flatulence (90% total: 70% peri-procedurally, 40% during follow-up), abdominal pain/cramping (60% total: 50% peri-procedurally, 60% during follow-up), diarrhea (60% total: 40% peri-procedurally, 5 during follow-up), blood in stool (30% total: 20% peri-procedurally, 30% during follow-up), fever (20%, all occurred peri-procedurally), fatigue (20% total: 10% peri-procedurally, 20% during follow-up), inability to retain the enema (10%), and lower back pain due to positioning during FMT (10%). Although not related to FMT, cervical lymphadenopathy and headache, nausea, or vomiting from concurrent medication use was also reported. All of the adverse events related to FMT were self-limiting and did not require intervention from health care providers (except fever).

4.4 Key Question 4: Differential Efficacy and Harms in Subpopulations

Number of studies retained

For this key question, RCTs that stratified on patient characteristics of interest, permitting evaluation of effect modification were considered for inclusion. Subgroups of interest included (but were not limited to): age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation. All RCTs included to evaluate the efficacy or safety of FMT versus comparators of interest were assessed.

4.4.1 Clostridium difficile Infection (CDI)

4.4.1.1 Type of Preparation: Fresh versus Frozen Feces for FMT

Differential efficacy was evaluated by one RCT[78] that compared frozen and fresh feces for FMT in patients with recurrent or refractory CDI. Subgroups specified *a priori* were age (<65 vs. ≥65 years), hospitalization status at time of procedure (inpatient vs. outpatient), and *C. difficile* strain type (non-BI/027 vs. BI/027). Other subgroups analyzed (and not clearly specified *a priori*) included baseline CDI severity (mild vs. moderate vs. severe), setting of first CDI (hospital vs. community), and *C. difficile* toxin status at baseline. No formal test for interaction was reported. Trial details and results are in section 3.2.2.3. The trial was found to be at moderately low risk of bias; methodological limitations included failure to adhere to the intention to treat principle and failure to control for potentially confounding differences in baseline characteristics (including inpatient status, mild CDI, severe CDI). Patients were randomized to infusion of either frozen (n=114) or fresh (n=118) feces, which was performed by retention enema. Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence through 13 weeks.

For the overall population, there were no differences between frozen versus fresh groups in achieving cure within 13 weeks of up to two FMT procedures.[78] None of the subgroups analyzed appeared to modify this outcome based on overlap of the 95% confidence intervals, with the possible exception of hospitalization status at the time of FMT: inpatients who received frozen feces responded similarly to those infused with fresh feces (69% vs. 75% (RD -6% (95% CI -23%, 10%)), while outpatients who received frozen feces were significantly more likely to achieve cure than those who were infused with fresh feces (82% vs. 65% (RD 17% (95% CI 1%, 34%)).

Table 23. Frozen vs. Fresh FMT for recurrent or refractory CDI: Heterogeneity of Treatment Effect for Cure through 13 weeks after the last FMT (≤2 FMT procedures)

RCT	Subgroup category	Subgroup	FMT: Frozen Feces	FMT: Fresh Feces	RD (95% CI)*	Interaction p-value
Lee 2016	Overall population	(none)	75.0% (81/108)	70.3% (78/111)	4.7% (-7.1%, 16.5%)	NA
	Age	<65 years	82% (22/27)	63% (17/27)	19% (-5%, 42%)	NS†
		≥65 years	73% (59/81)	73% (61/84)	0% (-13%, 14%)	
	Hospital admission status at time of FMT	Inpatient	69% (35/51)	75% (45/60)	-6% (-23%, 10%)	NS†
		Outpatient	82% (46/56)	65% (33/51)	17% (1%, 34%)	
	Baseline CDI severity	Mild	81% (33/41)	85% (28/33)	-4% (-22%, 13%)	NS†
		Moderate	69% (34/49)	57% (29/51)	13% (-6%, 31%)	
		Severe	78% (14/18)	78% (21/27)	0% (-25%, 25%)	
	Setting of primary episode of CDI	Health care	75% (49/65)	72% (53/74)	4% (-11%, 18%)	NS†
		Community	74% (29/39)	66% (23/35)	9% (-12%, 30%)	
	Strain type	Non-BI/027	75% (15/20)	90% (18/20)	-15% (-38%, 8%)	NS†
		BI/027	67% (10/15)	71% (10/14)	-5% (-38%, 29%)	
		Not tested	77% (56/73)	65% (50/77)	12% (-3%, 26%)	
	CD toxin *tcdB* at baseline	Positive	79% (34/43)	77% (34/44)	2% (-16%, 19%)	NS†
		Negative	71% (44/62)	65% (40/62)	6% (-10%, 23%)	

CD: *Clostridium difficile*; CDI: *Clostridium difficile* infection; NA: not applicable; NS: p>0.05; RD: risk difference; tcdB: *C. difficile* toxin B gene

*Calculated

†Interaction p-value not reported by the study; estimated to be >0.05 due to substantial overlap in the confidence intervals for the subgroups of interest.

4.5 Key Question 5: Cost effectiveness

Number of studies retained

Five cost utility analyses (CUA)[71,75,88,132,133] were identified that met the inclusion criteria; all evaluated the impact of FMT compared with antibiotic(s) in patients with CDI. No full economic evaluations were conducted on patients with IBD.

4.5.1 Cost Effectiveness of FMT for CDI

Study characteristics

Study characteristics are summarized in Table 24; detailed abstractions of study characteristics, assumptions, and results can be found in Appendix Table H1.

All five studies were cost utility analyses and were conducted in the US[71,132,133], Canada[75], or Australia[88]. All used a hypothetical adult population. While one[132] assumed patients were treated for a first CDI, the other four assumed patients had recurrent CDI[71,75,88,133]. All five studies compared FMT via colonoscopy to vancomycin therapy; three[71,75,88] also evaluated additional infusion modalities (NG, duodenal, and/or enema infusion), while metronidazole and/or fidaxomicin were also assessed as alternative antibiotic therapies by three studies[71,75,132].

The majority of studies were conducted from a payer perspective; although one[71] was stated to be conducted from a societal perspective, the societal impact of productivity loss was not accounted for in their model. The time horizon varied from 90 days to one year across four studies[71,75,132,133]. Decision trees were used by four of the studies[71,75,132,133], while one study[88] employed Markov modeling. Results from sensitivity analysis were reported by four studies and included model sensitivity analysis (in which different scenarios were evaluated) in two studies[71,75], one-way sensitivity analysis in four studies[71,75,132,133], two-way sensitivity analysis in one study[75], and probabilistic sensitivity analysis in three studies[75,132,133].

The clinical effectiveness outcome was reported in terms of quality-adjusted life years (QALY), the values for which were derived from published literature (e.g., RCTs, cohort studies, and/or case series). The components used to derive the QALY included cure, recurrence following initial cure, mortality, adverse events, colectomy, fulminant colitis, hospitalization, and ileostomy. Assumptions regarding cure and/or recurrence rate are compared to results from studies included in this HTA in Appendix Table H2. Of note, the assumed cure rates following colonoscopic FMT (range, 81.3% to 94.5% from four economic studies[71,88,132,133]) were higher than those reported following a single FMT procedure by the two RCTs[25,142] included in this HTA that employed that route (65% to 80% at 2 to 2.5 months), though one retrospective cohort study[117] reported three-month cure rates to be 96% following a single procedure. Assumed cure rates for recurrent CDI following FMT (any route) as reported by three economic analyses[71,88,133] ranged from 81.3% to 94.5%. Overall, cure rates for recurrent CDI at two to three months following a single FMT (any route) as reported by studies included in this HTA ranged from 51.5% to 80% as reported by four RCTs[25,78,131,142], 93% to 96% as reported by two cohort studies[117,136], and 52% to 94% across eight case series of adult patients[4,21,51,67,70,85,98,100,111]. In addition, the cure rates following the first occurrence of CDI was 63% at one month as reported by one cohort study[74]. Assumed cure rates following vancomycin ranged from 30.8% to 91.6% across four economic studies[71,88,132,133], while the data from two RCTs[25,131] included in this HTA reported cure rates of 26% to 27% at 2.5 months.

Costs were reported in 2011 to 2015 US, Canadian, or Australian dollars. Cost data were derived from a variety of sources, including CMS in all three studies[71,132,133] conducted from a US perspective, national databases, market prices, and published cost studies. The components of cost data included that of the treatment (typically to include donor testing for FMT), hospitalization for recurrent CDI, adverse events, and outpatient visits. Discounting was used by one study that reported "long-term" results.[88]

Four[71,75,132,133] of the CUA were relatively well-conducted, with QHES scores ranging from 71 to 89; one of the studies[88] had more methodological limitations, with a QHES score of 54 (Appendix Table E4). Methodological limitations (in decreasing order of frequency) included failure to describe data abstraction methodology[71,75,88,132,133], short-term (or unclear) time horizons only[75,88,132,133], no discussion of direction or magnitude of potential biases[71,88,132,133], failure to use available RCT data for clinical outcome estimates[132,133], no clear disclosure of funding[132], unclear analytic perspective[88], failure to report results of sensitivity analysis[88], unclear economic model and methodology[88], and failure to discuss study limitations[88].

Results

Base Case

FMT via colonoscopy was found to be dominant[133] or more cost effective[71,75,88] compared to vancomycin in all four studies of patients with recurrent CDI. Conclusions were similar when comparing FMT to metronidazole[71,75] or fidaxomicin[71,75]. For FMT using other infusion methods (duodenal tube[88], NG tube[75], or enema[75]), two studies found that FMT was dominant, but one study[71] found in model

sensitivity analysis that FMT via duodenal infusion or enema were dominated (i.e., more costly and less effective) by vancomycin.

For the initial CDI occurrence, one study[132] found that FMT via colonoscopy was dominant over vancomycin alone; this FMT modality was more costly but more effective than metronidazole ($124,964/QALY) through 90 days.

Sensitivity Analyses
Results of the various sensitivity analyses are summarized by study in Table 24. In general, sensitivity analyses supported the conclusion that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI.

Model sensitivity analyses varied the scenarios. Of note, one study[71] found that FMT via duodenal infusion or enema was dominated by vancomycin, while another study[75] found that FMT via enema was more cost effective than metronidazole. Older patient age and fidaxomicin patent status had no effect on the conclusion that FMT via colonoscopy dominated all antibiotic therapies for recurrent CDI.[75]

One-way sensitivity analysis was performed by four studies[71,75,132,133], in which individual outcome, cost, and utility value parameters were varied within reported ranges. For initial or recurrent CDI, FMT via colonoscopy remained dominant in most analyses, although this conclusion was sensitive to cure rates and procedure costs (see Table 24). One study reported similar results from two-way sensitivity analyses.[75]

Probabilistic sensitivity analysis results were reported by three studies.[75,132,133] For recurrent CDI, FMT was dominant in 87% of 10,000 second order Monte Carlo simulations at a willingness to pay threshold of $50,000 per QALY in one study[75]; another study[133] reported that FMT was dominant in 100% of such simulations but the willingness to pay threshold was unclear. In the CUA of initial CDI, metronidazole was dominant in 55% and FMT dominant in 38% of 10,000 second order Monte Carlo simulations at a willingness to pay threshold of $100,000 per QALY.[132]

Conclusions and Limitations
In general, results from the five included CUA suggested that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI.

Limitations included lack of long-term follow-up, use of hypothetical populations, use of nonrandomized studies for assumptions regarding clinical outcomes, assumed high cure rates and relatively low recurrence rates following FMT, and no analysis of severe and/or complicated CDI. Overall, the studies were relatively well-conducted.

Table 24. Cost Utility Analyses in CDI patients: Study Characteristics and Results

	Varier 2014	Konijeti 2014	Lapointe-Shaw 2016	Merlo 2016	Varier 2015
Study Characteristics					
Population	Adults with initial CDI; hypothetical population.	Adults (median age 65) with 1st recurrence of mild/moderate CDI; hypothetical population.	Adults (age 70) with 1st recurrence of CDI; hypothetical population.	Adults (age 65) with ≤1 recurrence of CDI; simulated cohort of 1000 patients.	Adults with 3rd recurrence of CDI; hypothetical population.
Intervention(s)	FMT via colonoscopy	FMT (+ vancomycin) via colonoscopy (base case) …….. Alternative modes for model SA only: • FMT (+ vancomycin) via duodenal infusion • FMT (+ vancomycin) via enema	1) FMT (+ vancomycin) via colonoscopy 2) FMT (+ vancomycin) via NG tube 3) FMT (+ vancomycin) via enema	1) FMT (+ bowel lavage, vancomycin) via colonoscopy 2) FMT (+ bowel lavage, vancomycin) via nasoduodenal infusion	FMT via colonoscopy
Comparator(s)	(a) Vancomycin (b) Metronidazole	(a) Vancomycin (b) Metronidazole (c) Fidaxomicin	(a) Vancomycin + vancomycin taper (b) Metronidazole + vancomycin taper (c) Fidaxomicin + vancomycin taper	Vancomycin	Vancomycin
Country	USA	USA	Canada	Australia	USA
Funding	NR (authors declared no CoI)	Grant	None	None	Grant
Study design	CUA	CUA	CUA	CUA	CUA
Perspective	Payer	Societal	Payer (Ontario Ministry of Health)	NR (appears to be payer)	Payer
Time horizon	90 days	1 year	18 weeks (with 6-week cycles)	"Long-term" (details NR) (with 10-day cycles)	90 days
Analytic model	Decision tree	Decision tree	Decision tree with Markov processes	Markov	Decision tree
Effectiveness outcome	QALY	QALY	QALY over lifetime**	QALY	QALY

	Varier 2014	Konijeti 2014	Lapointe-Shaw 2016	Merlo 2016	Varier 2015
Components of effectiveness outcome	Cure, recurrence, AEs, mortality, fulminant colitis	Cure, recurrence, development of severe CDI, colectomy, mortality	Recurrence, mortality, hospitalization	Cure, recurrence, mortality, colectomy, ileostomy, reinfection with CDI	Cure, recurrence, AEs, mortality, fulminant colitis
Source for effectiveness data	Published literature (various)	Published literature (various), including van Nood RCT[131]	Published literature (various), including van Nood RCT[131]	Published literature (various), including van Nood, Cammarota, and Youngster RCTs[25,131,142]	Published literature (various)
Costing year	2011	2012/2013	2014	2015	2011
Currency	US $	US $	Canadian $	Australian $	US $
Cost sources	CMS Published cost studies	CMS (for FMT); all other costs from Consumer Price Index	Published literature, Ontario Drug Benefit, Toronto hospitals, Statistics Canada, Ontario Schedule of Benefits, Ontario Case Costing Initiative	National databases, market prices, Pharmaceutical Benefits Schedule, National Hospital Cost Data Collection, Queensland Health wage rates, Medicare Benefits Schedule	CMS Published cost studies
Components of cost data	Cost of treatment, testing for recurrent CDI, vancomycin taper for recurrent CDI, adverse events of FMT	Cost of treatment (including donor testing), hospitalization for recurrent CDI, f/u outpatient visits	Cost of treatment (including donor testing), outpatient visits, hospitalization	Cost of treatment (including donor testing), pretreatment, hospitalization for recurrence, colectomy, ileostomy closure	Cost of treatment, testing for recurrent CDI, vancomycin taper for recurrent CDI, adverse events of FMT, death
Discounting	NR	NR	5% over 5 years (applicable to capital costs for stool preparation equipment only)	5%	None
Sensitivity analysis	One-way SA† Probabilistic SA§	Model SA* One-way SA†	Model SA* One-way SA† Two-way SA‡ Probabilistic SA§	NR††	One-way SA† Probabilistic SA§
QHES	71/100	89/100	88/100	54/100	74/100
Results:					
BASE CASE					
Cost / QALY of intervention(s)	$1669 / 0.242	$3149 / 0.8719	1) $5246 / 9.40** 2) $5935 / 9.15**	1) $4045 (95% CI -$44, $8124) less than	$1669 / 0.242

	Varier 2014	Konijeti 2014	Lapointe-Shaw 2016	Merlo 2016	Varier 2015
			3) $5667 / 9.26**	vancomycin 2) $4094 (95% CI $26, $8161) less than vancomycin	
Cost of comparator(s)	(a) $1890 / 0.241 (b) $1167 / 0.238	(a) $2912 / 0.8580 (b) $3941 / 0.8292 (c) $4261 / 0.8653	(a) $5929 / 9.03** (b) $5386 / 9.09** (c) $7319 / 9.16**	NR	$3788 / 0.235
ICER (FMT vs. comparator)	(a) FMT dominant (b) $124,964/QALY	(a) $17,016 (so FMT cost-effective at WTPT of $25,000) (b) FMT dominant (c) FMT dominant	FMT (+ vancomycin) via colonoscopy dominant over all alternatives (including FMT via NG tube or enema)	FMT via either route vs. vancomycin: 1.2 (95% CI 0.1, 2.3) QALY, or 1.4 (95% CI 0.4, 2.4) life years saved	FMT dominant
SENSITIVITY ANALYSIS					
Model SA*	NR	FMT via duodenal infusion or enema were both dominated (i.e., more cost, less effective) by vancomycin. If available, FMT via colonoscopy is the most cost-effective treatment.	FMT (+ vancomycin) via colonoscopy dominant over all alternatives in scenarios where patient 10 years older or fidaxomicin available as generic drug; in scenario of 2 cycles only with recurrence after first cycle, FMT via colonoscopy was cost effective (ICER $514) compared to metronidazole; if no colonoscopy available, FMT via enema was cost effective (ICER $1708) compared to metronidazole	NR	NR
One-way SA†	Metronidazole dominated both FMT & vancomycin if cure rate >90%. FMT dominated if cost <$584, metronidazole cost >$559, or metronidazole cure rate <71%.	FMT dominant if: cure rate for FMT>88.4%, cure rate for vancomycin ≤95.5%, recurrence rate for FMT <14.9%, recurrence rate for vancomycin <27.2%, or FMT cost ≤$2724.	FMT (+ vancomycin) via colonoscopy dominant over all alternatives in all analyses except two: FMT via enema dominant if recurrence <8.7% for this treatment or if cost of FMT via colonoscopy >$8062 per infusion	NR	FMT dominant if cure rate for vancomycin ≤90% & FMT ≤$3205

	Varier 2014	Konijeti 2014	Lapointe-Shaw 2016	Merlo 2016	Varier 2015
Two-way SA‡	NR	NR	FMT (+ vancomycin) via colonoscopy dominant over all alternatives in all analyses except for FMT via enema as stated for one-way SA	NR	NR
Probabilistic SA§	Metronidazole dominant in 55% and FMT dominant in 38% of 10,000 2nd-order Monte Carlo simulations using WTPT of $100,000/QALY.	NR	FMT dominant in 87% 10,000 2nd-order Monte Carlo simulations using WTPT of $50,000/QALY	NR	FMT dominant in all 10,000 2nd-order Monte Carlo simulations

AE: adverse event; CDI: Clostridium difficile infection; CMS: Centers for Medicare and Medicaid Services; CUA: cost utility analysis; NG: nasogastric; NR: not reported; QALY: quality adjusted life year; QHES: Quality of Health Economic Studies; QoL: quality of life; SA: sensitivity analysis; WTPT: willingness to pay threshold

*Model sensitivity analysis:

- Konijeti: three additional scenarios were compared:
  1. FMT via duodenal infusion vs. all three antibiotic arms
  2. FMT via enema vs. all three antibiotic arms
  3. FMT delivery via any of the three routes (colonoscopy, duodenal infusion, enema) vs. all three antibiotic arms
- Lapointe-Shaw: different scenarios tested:
  1. Patient 10 years older
  2. Fidaxomicin becomes off-patent (i.e., available as generic drug)
  3. No colonoscopy available
  4. Two cycles only (single recurrence after first cycle)

†One-way sensitivity analysis:

- Konijeti: included variations on outcome rates, costs, and utility values
- Lapointe-Shaw: variations on all parameters within reported ranges
- Varier 2014; Varier 2015: individual variations of "several key parameters" (details NR), including cure rate and treatment cost

‡Two-way sensitivity analysis:

- Lapointe-Shaw: variations of parameter found to have greatest impact on base-case results

§Probabilistic sensitivity analysis:

- Lapointe-Shaw: variations of all parameters in 10,000 Monte Carlo cohort-based simulations
- Varier 2014; Varier 2015: variations of all parameters (cure, fulminant colitis, AEs from FMT, death from FMT, costs, utility values) in 10,000 second order Monte Carlo simulations

**Lapointe-Shaw reported QALY for patient's remaining life expectancy (done by adding QALY estimated from model to the QALY-weighted expected life years remaining)

††Merlo stated that probabilistic sensitivity analysis was performed, however no results for this analysis were reported.

5. Strength of Evidence (SoE) Summary Tables

The following summaries of evidence have been based only on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by comparator. Details of other outcomes are available in the report.

5.1 Strength of Evidence Summary: FMT versus Vancomycin for Recurrent CDI

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
FMT + bowel lavage vs. vancomycin ± bowel lavage for recurrent CDI									
Cure* after single treatment	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N=82	Yes[1] (-1)	No	No	Yes[3] (-1)	Pooled RD 45% (95% CI 25%, 64%) Conclusion: After a single treatment, significantly more FMT patients achieved cure through 2.5 months than those in the vancomycin group.	⊕⊕◯◯ LOW
Additional FMT procedure(s)†	≤2.5 mos.	1 RCT (van Nood)	N=43	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	RD -46% (95% CI -73%, -19%) Conclusion: In 1 RCT, FMT for recurrent CDI was used in significantly fewer patients in the FMT group (24% (4/17) vs. 69% (16/26) in the vancomycin group); cure was achieved in 3/4 and 15/17 of these patients (respectively). (The other trial did not report comparative data: while 30% (6/20) of FMT patients underwent one or more additional FMTs, and 5/6 achieved cure; patients in the vancomycin group were not offered FMT.)	⊕⊕◯◯ LOW
Mortality attributed to CDI	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N=79	Yes[1] (-1)	No	No	Yes[3] (-1)	Pooled RD 0% (95% CI -9%, 8%) Conclusion: No difference between groups. One trial (Cammarota) reported 2 deaths from CDI in each group; the other trial (van Nood) reported 0 deaths in both groups.	⊕⊕◯◯ LOW
All-cause mortality	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N=79	Yes[1] (-1)	No	No	Yes[3] (-1)	Pooled RD -4% (95% CI -14%, 7%)) Conclusion: No difference between groups. One trial (Cammarota) reported 2 deaths from CDI in each group; the other trial (van Nood) reported 0 deaths in the FMT group and 1 death in the vancomycin	⊕⊕◯◯ LOW

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								group.	
All-cause mortality	≤8 mos.	1 RCT (Cammarota)	N=36	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	RD -23% (95% CI -51%, 6%)) Conclusion: No difference between groups. There were 3 deaths in the FMT group (2 of which from CDI) and 6 in the vancomycin group (2 of which from CDI).	⊕⊕◯◯ LOW

CDI: *Clostridium difficile* infection; CI: confidence interval; ; RD: risk difference

* Cure was defined as the absence of CDI-related diarrhea (loose or watery stools ≥3 times per day for ≥2 consecutive days, or ≥8 times within previous 2 days) plus two (Cammarota) or three (van Nood) negative stool tests for *C. difficile* toxin.

†In both trials, patients in the FMT group were offered repeat FMT upon relapse of CDI: feces from a different donor was used in one trial (van Nood); the other trial (Cammarota) repeated FMT every 3 days until resolution was achieved. Recurrence of CDI following vancomycin (± bowel lavage) was handled differently between the trials: while the Cammarota trial did not treat control group patients with FMT (in fact, it was unclear what (if any) treatment was offered these patients); the van Nood trial offered FMT off-protocol to these patients following recurrence of CDI.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size

5.2 Strength of Evidence Summary: FMT versus Placebo for IBD (UC)

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
FMT* vs. placebo* for IBD (UC)									
Clinical remission + endoscopic response†	1.75 mos.	1 RCT (Moayyedi)	N=75	No	No	No	Yes[3] (-1)	RD 18% (95% CI 3%, 34%) Conclusion: While slightly more FMT than placebo* patients achieved this outcome (24% vs. 5%), the trial was ended early due to futility. A second smaller trial at moderately high risk of bias due to a number of methodological flaws (Rossen, N=48) reported a similar direction of effect, although the results did not reach statistical significance due to small sample size (30% vs. 20%, RD 10% (95% CI -14%, 35%) and was also ended early because of futility.	⊕⊕⊕○ MODERATE
	12 mos.	1 RCT (Moayyedi)	N=38	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: No firm conclusions can be made. This outcome was achieved by 21% (8/38) of patients in the FMT group but was not evaluated in the placebo group.	⊕○○○ INSUFFICIENT
Clinical remission‡	3 mos.	1 RCT (Rossen)	N=48	Yes[2] (-1)	Unknown	No	Yes[3] (-1)	RD -2% (95% CI -28%, 25%) Conclusion: No difference between FMT and placebo* groups (30% vs. 32%).	⊕⊕○○ LOW
Clinical response§	1.75 mos.	1 RCT (Moayyedi)	N=75	No	No	No	Yes[3] (-1)	RD 15% (95% CI -6%, 36%) Conclusion: No difference between FMT and placebo* groups (39% vs. 24%). A second smaller trial at moderately high risk of bias due to a number of methodological flaws (Rossen, N=48) reported similar results at 3 months (48% vs. 52%, RD -4% (95% CI -32%, 24%)).	⊕⊕⊕○ MODERATE
Additional procedures	3 mos.	1 RCT (Rossen)	N=48	Yes[2] (-1)	Unknown	No	Yes[3] (-1)	RD 10% (95% CI -11%, 31%) Conclusion: No difference between FMT and placebo* groups (22% vs. 12%) in the need for rescue therapy (not defined) for ongoing disease flare.	⊕⊕○○ LOW

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
	12 mos.	1 RCT (Moayyedi)	N=38	Yes[1] (-1)	Unknown	No	Yes[3,4] (-2)	Conclusion: No firm conclusions can be made. One patient (3%) in the FMT group required treatment with infliximab for continuing symptoms; this outcome was not evaluated in the placebo group	⊕◯◯◯ INSUFFICIENT
All-cause mortality	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT

CI: confidence interval; IBD: inflammatory bowel disease; NA: not applicable; NR: not reported; RD: risk difference; UC: ulcerative colitis

*Treatment groups:

- Moayyedi: FMT vs. water (placebo) via retention enema.
- Rossen: FMT + bowel lavage using donor feces vs. autologous feces (placebo).

† Clinical remission plus endoscopic response definitions:

- Moayyedi: full Mayo Clinic score <3 (range 0-12 (worst)) and complete healing of the mucosa during flexible sigmoidoscopy/ endoscopic Mayo Clinic score of 0
- Rossen 2015: SCCAI score ≤2 (range 0-19 (worst)) and ≥1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum (as compared with baseline sigmoidoscopy) 12 weeks after the first treatment.

‡Defined as a SCCAI score ≤2. At 12 weeks, 0% (0/23) vs. 8% (2/25) in the FMT vs. control group were no longer in remission after being in remission at week 6 and 4% (1/23) vs. 8% (2/25), respectively, were in remission after not being in remission at week 6.

§Clinical response definitions:

- Moayyedi: reduction in full Mayo clinic score of ≥3 points (range 0-12 (worst)).
- Rossen 2015: reduction of ≥1.5 points on the SCCAI (range 0-19 (worst)).

Reasons for downgrading:

1. Serious risk of bias: the study violated one or more of the criteria for good quality RCT related to the outcome reported: for 12 month data, patients were not blinded.
2. Serious risk of bias: the study violated one or more of the criteria for good quality RCT related to the outcome reported
3. Inconsistency: differing estimates of effects across trials
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or wide confidence interval
5. Imprecise effect estimate: unknown confidence interval (no results reported for placebo group)

5.3 Strength of Evidence Summary: Comparisons of FMT Administration Routes

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
CDI: Colonoscopic FMT vs. Nasogastric (NG) FMT									
Cure* after single treatment	≤2 mos.	1 RCT (Youngster)	N=20	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	RD 20% (95% CI -19%, 59%) Conclusion: No firm conclusions can be made. No statistical difference between colonoscopic and NG tube infusion (80% (8/10) vs. 60% (6/10)).	⊕◯◯◯ INSUFFICIENT
Additional FMT procedure(s)	≤2 mos.	1 RCT (Youngster)	N=20	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	RD -10% (95% CI -48%, 28%) Conclusion: No firm conclusions can be made. No statistical difference between groups (20% (2/10) vs. 30% (3/10)); cure was achieved in 2/2 and 2/3 of these patients (respectively).	⊕◯◯◯ INSUFFICIENT
Mortality attributed to CDI	≤2 mos.	1 RCT (Youngster)	N=20	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	RD 0% Conclusion: No firm conclusions can be made. No events in either group (0% vs. 0%).	⊕◯◯◯ INSUFFICIENT
All-cause mortality	≤6 mos.	1 RCT (Youngster)	N=20	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	Conclusion: No firm conclusions can be made. Comparative data not reported. Two patients (10%) died through 6 months f/u; the treatment group was not reported.	⊕◯◯◯ INSUFFICIENT
IBD: Comparisons of FMT Administration Routes									
Any	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT

CDI: *Clostridium difficile* infection; CI: confidence interval; F/U: follow-up; IBD: inflammatory bowel disease; NG: nasogastric; RD: risk difference

* Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size and confidence interval includes both negligible effect and appreciable benefit or harm for treatment group

5.4 Strength of Evidence Summary: Comparisons of Timing of FMT Administration

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
CDI: "Timely" vs. "Delayed" FMT (i.e., following 2 vs. ≥3 recurrences of CDI)									
Cure* after single treatment	≤3 mos.	1 retro. cohort study (Waye)	N=75	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: No firm conclusions can be made. No difference between "timely" versus "delayed" FMT (i.e., FMT after 2 vs. ≥3 CDI recurrences) (94% (28/30) vs. 93% (42/45), p=0.93).	⊕◯◯◯ INSUFFICIENT
Additional FMT procedure(s)	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT
Mortality attributed to CDI	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT
All-cause mortality	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT
IBD: Comparisons of timing of FMT Administration									
Any	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT

CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease

* Cure was not clearly defined. The study did define recurrence of CDI as diarrhea (≥3 loose stools per day) plus a positive stool toxin test occurring in less than two months from the time the previous course of antibiotics was completed.

Reasons for downgrading:

4. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
5. Inconsistency: differing estimates of effects across trials
6. Imprecise effect estimate for a dichotomous outcome: small sample size

5.5 Strength of Evidence Summary: Comparisons of Fecal Preparations

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
CDI: FMT using Frozen vs. Fresh Feces									
Cure* after single treatment	≤3.25 mos.	1 RCT (Lee)	N= 219	Yes[1] (-1)	No	No	Yes[3] (-1)	RD 2.3% (95% CI -10.9%, 15.6%) Conclusion: No difference between frozen vs. fresh feces for FMT infusion (52.8% (57/108) vs. 50.5% (56/111)).	⊕⊕◯◯ LOW
Additional FMT procedure(s)	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT
Mortality attributed to CDI	≤3.25 mos.	1 RCT (Lee)	N= 219	Yes[1] (-1)	Unknown	No	Yes[4] (-1)	RD 0.1% (95% CI -3.5%, 3.6%) Conclusion: No difference between frozen vs. fresh feces for FMT infusion (1.9% (2/108) vs. 1.8% (2/111)).	⊕⊕◯◯ LOW
All-cause mortality	≤3.25 mos.	1 RCT (Lee)	N= 219	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	RD -6.2% (95% CI -13.5%, 1.2%) Conclusion: No statistical difference between frozen vs. fresh feces for FMT infusion, although the incidence of death from any cause was slightly lower in the frozen feces group (5.6% (6/108) vs. 11.7% (13/111)).	⊕⊕◯◯ LOW
IBD: Comparisons of fecal preparations									
Any	Any	0 studies						No evidence	⊕◯◯◯ INSUFFICIENT

CDI: *Clostridium difficile* infection; CI: confidence interval; IBD: inflammatory bowel disease; RD: risk difference

* Cure was defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: confidence interval includes both negligible effect and appreciable benefit or harm for treatment group
4. Imprecise effect estimate for a dichotomous outcome: rare outcome and small sample size

5.6 Strength of Evidence Summary: Safety of FMT for CDI

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
FMT + bowel lavage vs. vancomycin ± bowel lavage for recurrent CDI: FMT-related adverse events									
Serious adverse events	≤2.5 mos.	2 RCTs (van Nood, Cammarota)	N= 82	Yes[1] (-1)	No	No	Yes[3] (-1)	RD 0% Conclusion: No serious adverse events (including death) occurred in either treatment group.	⊕⊕◯◯ LOW
Non-serious adverse events	≤2.5 mos.	1 RCT (van Nood)	N= 43	Yes[1] (-1)	Unknown	No	Yes[3] (-1)	Conclusion: The following non-serious adverse events occurred with statistically similar frequency between FMT and vancomycin groups as measured between the first day after treatment and 2.5 months follow-up: • Constipation (19% vs. 12%, RD 7% (95% CI -16%, 30%) • Infection (13% vs. 4%, RD 9% (95% CI -9%, 26%)) • Gastrointestinal complaints (0% vs. 8%, RD -8% (95% -18%, 3%)) • Indigestion (0% vs. 4%, RD -4% (95% CI -11%, 4%)) • Nausea (0% vs. 4%, RD -4% (95% CI -11%, 4%)) • Belching (0% vs. 0%) • Vomiting (0% vs. 0%) • Abdominal cramps or pain (0% vs. 0%) • Diarrhea (0% vs. 0%)	⊕⊕◯◯ LOW
Colonoscopic FMT vs. Nasogastric (NG) FMT for recurrent or refractory CDI: FMT-related adverse events									
Serious adverse events	≤2-6 mos.	1 RCT (Youngster)	N= 20	Yes[1] (-1)	Unknown	No	Yes[3] (-2)	RD: 0% Conclusion: No firm conclusions can be made. No serious adverse events were attributed to FMT over 2 months of follow-up, including death which was measured through 6 months.	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	0 studies						No comparative evidence	⊕◯◯◯ INSUFFICIENT

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
"Timely" vs. "Delayed" FMT (i.e., following 2 vs. ≥3 recurrences of CDI): FMT-related adverse events									
Serious adverse events	Any	0 studies						No comparative evidence	⊕◯◯◯ INSUFFICIENT
Non-serious adverse events	Any	0 studies						No comparative evidence	⊕◯◯◯ INSUFFICIENT
FMT using Frozen vs. Fresh Feces for recurrent CDI: FMT-related adverse events									
Serious adverse events	≤3.25-12 mos.	1 RCT (Lee) 1 cohort study (Satokari)	N= 261	Yes[1] (-1)	No	No	Yes[3] (-1)	RD: 0% Conclusion: No serious adverse events (including death) were attributed to FMT using feces prepared by either method as reported by the RCT (N=219) and cohort study (N=42).	⊕⊕◯◯ LOW
Non-serious adverse events	≤24 hours	1 RCT (Lee)	N= 232	Yes[1] (-1)	No	No	Yes[5] (-1)	Conclusion: One trial reported the following mild to moderate symptoms occurred similarly between groups, however data were not stratified by groups and patient numbers were not reported: • Transient diarrhea: 70% • Abdominal cramps: 10% • Nausea: <5%	⊕⊕◯◯ LOW
Non-serious adverse events	≤12 mos.	1 cohort study (Satokari)	N= 42	Yes[1] (-1)	No	No	Yes[3] (-1)	Conclusion: No firm conclusions can be made. A mild short-term fever occurred in more frozen vs. fresh FMT patients (12% (2/17) vs. 0% (0/25), though the difference was not significant (p=0.08).	⊕◯◯◯ INSUFFICIENT
Noncomparative: FMT-related adverse events (any route, preparation)									
Serious adverse events	≤2-24 mos.	1 cohort study (Lagier) 8 case series (Rubin,	N= 640	Yes[1] (-1)	Unknown	No	Yes[3,5] (-2)	Conclusion: No firm conclusions can be made. For the studies in which no comparative data were reported, serious FMT-related adverse events were relatively uncommon across 1 cohort study (33 FMTs), and 8 case series	⊕◯◯◯ INSUFFICIENT‡

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
		Kelly, Brandt, Mattila, Orenstein, Agrawal, Patel, Lee)						(N=607). The following details were reported: • *Mortality attributed to FMT* - 8 case series: 0.2% (1/607)* • *"Serious adverse events":* ○ 1 cohort study: 0% (0/49) ○ 3 case series: 0% (0/198) • *Microperforation of small bowel†:* ○ 1 case series: 3% (1/34) • *Acute cardiac insufficiency:* ○ 1 cohort study: 3% (1/33 FMTs); occurred on day of procedure, described by the study as a minor event. • *Hospitalization for FMT-related abdominal pain:* • 1 case series: 1% (1/80); pain was self-limited • *Hospitalization for FMT or CDI-related abdominal pain:* 1% (1/80) • 1 case series: 1% (1/80)	
Non-serious adverse events	≤48 hours	3 RCTs (van Nood, Cammarota, Youngster) 1 cohort study (Lagier) 2 case series (Kelly, Kronman)	N= 146 (+ 33 FMTs)	Yes[1] (-1)	Unknown	No	Yes[5] (-1)	Conclusion: For the studies in which no comparative data were reported, the following non-serious FMT-related adverse events were documented across 3 RCTs (N=56), 1 cohort study (33 FMTs), and 3 case series (N=90). The following details were reported: • *Diarrhea: 73% - 94%* • 2 RCTs: 94% (34/36 across both RCTs) • 1 cohort study: 73% (24/33 FMTs) • *Abdominal cramps: 47%* • 2 RCTs: 47% (17/36 across 2 RCTs) • *Abdominal discomfort/pain: 4% - 39%* • 2 RCTs: 39% (14/36 across 2 RCTs) • 1 case series: 4% (3/80) (with bloating) • *Nausea: 3% - 6%*	⊕⊕◯◯ LOW§

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								• 1 RCT: 6% (1/16) • 1 cohort study: 3% (1/33 FMTs); nausea described as uncontrollable • *Fever: 1% - 5%* • 1 RCT: 5% (1/20) (2 days post-FMT, transient) • 1 case series: 1% (1/80) • *Belching: 19%* • 1 RCT: 19% (3/19) • *Minor mucosal tear during colonoscopy: 1%* • 1 case series: 1% (1/80) • *Mucoid stools: 10%* • 1 case series of pediatric patients: 10% (1/10 across both studies) • *Vomiting: 0% - 10%* • 1 RCT: 0% (0/16) • 1 case series of pediatric patients: 10% (1/10) • *Constipation: 0%* • 1 RCT: 0% (0/16) • *Dizziness with diarrhea: 6%* • 1 RCT: 6% (1/16) (patient had autonomic dysfunction) • *Refusal of nasogastric tube: 3%* • 1 cohort study: 3% (1/33 FMTs)	
Non-serious adverse events	>48 hours to 2.5 mos.	2 RCTs (Youngster, Lee) 8 case series (Kelly, Agrawal, Lee, Russell, Rubin, Orenstein, Jorup-Rostrum,	N= 763	Yes[1] (-1)	Unknown	No	Yes[5] (-1)	Conclusion: No firm conclusions can be made. For the studies in which no comparative data were reported, the following non-serious FMT-related adverse events were documented across 2 RCTs (N=252) and 8 case series (N=511). • *Abdominal discomfort: 2.7% - 60%* • 1 RCT: 20% (4/20) • 1 case series: 2.7% (4/146) • 1 case series of pediatric patients: 60%	⊕◯◯◯ INSUFFICIENT‡

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality

		Garborg)						(6/10)
								• *Excess flatulence: 25%*
								  • 1 RCT: 25% (~58/232)
								• *Constipation: 10% - 20%*
								  • 1 RCT: 20% (~46/232)
								  • 1 case series: 10% (9/94) (with excessive flatulence)
								• *Diarrhea: 4.4% - 10%*
								  • 2 case series: 4.4% (10/226 across both studies)
								  • 1 case series of pediatric patients: 10% (1/10)
								• *Mucoid stools: 10%*
								  • 1 case series of pediatric patients: 10% (1/10 across both studies)
								• *"Adverse events": 0% - 82%*
								  • 3 case series: 0% (0/147 across all 3 studies)
								  • 1 case series: 82% (28/34) patients experienced at least one adverse event through 6 months; many were unrelated to FMT.	

CDI: *Clostridium difficile* infection; NG: nasogastric; RD: risk difference

*The patient had esophageal cancer and cachexia, aspirated during sedation for the FMT procedure, and died the next day from respiratory failure.

†Microperforation occurred as a result of periprocedural biopsy in small bowel in region believed to have ischemic injury; patient recovered with conservative treatment.

‡Because the majority of the evidence is from nonrandomized studies and case series, the overall SoE started at "Low" and was then downgraded from there.

§Because the majority of the evidence is from RCTs, the overall SoE started at "High" and was then downgraded from there.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size, rare event
4. Imprecise effect estimate for a dichotomous outcome: confidence interval includes both negligible effect and appreciable benefit or harm for treatment group
5. Imprecise effect estimate for a dichotomous outcome: unknown confidence interval

5.7 Strength of Evidence Summary: Safety of FMT for IBD

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
FMT vs. placebo for IBD									
Serious adverse events	1.75-3 mos.	2 RCTs (Moayyedi, Rossen)	N= 123	Yes[1] (-1)	No	No	Yes[4] (-1)	Pooled RD 2% (95% CI -7%, 11%) Conclusion: Both RCTs reported no difference between groups in the overall incidence of "serious" adverse events (pooled, 8% (5/61) vs. 6% (4/62)), including: • Worsening colitis requiring colectomy: 0% (0/38) vs. 3% (1/37) (1 RCT) • New diagnosis of CD: 5% (2/38) vs. 3% (1/37) (1 RCT) • C. difficile infection: 3% (1/38) vs. 0% (0/37) (1 RCT) • Severe illness from CMV infection: 0% (0/23) vs. 4% (1/25) (1 RCT) • Severe small bowel CD, late abdominal pain, and operation for cervical carcinoma: not stratified by treatment group in one RCT Whether any of these events were directly related to FMT treatment is not clear.	⊕⊕◯◯ LOW
Non-serious adverse events	Peri-procedural	1 RCT (Rossen)	N=23	Yes[1] (-1)	Unknown	No	Yes[4] (-1)	78% (18/23) vs. 64% (16/25), RD 14% (-11%, 40%) Conclusion: There was no difference between groups in the overall incidence of FMT-related non-serious adverse events. • Increased stool frequency/diarrhea was more common with FMT (30% vs. 4%, RD 26% (95% CI 6%, 47%)). • Abdominal cramps were less common with FMT (0% vs. 24%, RD -24% (95% CI -41%, -7%))	⊕⊕◯◯ LOW

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								• All other peri-procedural events occurred with similar frequency between groups.†	
Noncomparative: FMT-related adverse events									
Serious adverse events	0.75-15 mos.	1 RCT (Moayyedi) 1 case series (Cui)	N=68	Yes[1] (-1)	Unknown	No	Yes[3,5] (-2)	Conclusion: No firm conclusions can be made. For the studies in which no comparative data were reported, serious adverse events were relatively uncommon across 1 RCT (N=38) and 1 case series (N=30): • *Colectomy for failure of UC therapy* (3% in one 1 RCT) • *Any serious adverse event* (0% in 1 case series)	⊕◯◯◯ INSUFFICIENT

Non-serious adverse events	Peri-procedural	2 case series (Cui, Kunde)	N=40	Yes[1] (-1)	Unknown	No	Yes[5] (-1)	Conclusion: No firm conclusions can be made. The following non-serious FMT-related adverse events were reported across two case series, one in an adult population (n=30) and one in a pediatric population (n=10):
								• *Diarrhea*:
								  • 23% (1 case series)
								  • 40% (1 case series of pediatric patients)
								• *Fever*:
								  • 7% (1 case series)
								  • 20% (1 case series of pediatric patients)
								• *Bloating/flatulence* (70% in 1 case series of pediatric patients)
								• *Abdominal pain/cramping* (50% in 1 case series of pediatric patients)
								• *Blood in stool* (20% in 1 case series of pediatric patients)
								• *Fatigue* (10% in 1 case series of pediatric patients)
								• *Inability to retain the enema*: (10% in 1 case
									⊕◯◯◯ INSUFFICIENT

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								series of pediatric patients) • *Lower back pain due to positioning during FMT* (10% in 1 case series of pediatric patients)	
Non-serious adverse events	1-15 mos.	2 case series (Cui, Kunde)	N=40	Yes[1] (-1)	Unknown	No	Yes[5] (-1)	Conclusion: No firm conclusions can be made. The following non-serious FMT-related adverse events were reported across two case series, one in an adult population (n=30) and one in a pediatric population (n=10): • *Pain (0% in 1 case series)* • *Fecal ileus (0% in 1 case series)* • *Abdominal pain/cramping (60% in 1 case series of pediatric patients)* • *Diarrhea (50% in 1 case series of pediatric patients)* • *Bloating/flatulence (40% in 1 case series of pediatric patients)* • *Blood in stool (30% in 1 case series of pediatric patients)* • *Fatigue* (20% in 1 case series of pediatric patients) • *Fever* (0% in 1 case series of pediatric patients)	⊕◯◯◯ INSUFFICIENT

CD: Crohn's disease; CI: confidence interval; CMV: Cytomegalovirus; ; IBD: inflammatory bowel disease; RD: risk difference; UC: ulcerative colitis

*Because the majority of the evidence is from nonrandomized studies and case series, the overall SoE started at "Low" and was then downgraded from there.

†Other periprocedural non-serious adverse events included (in decreasing order of frequency): abdominal murmurs, abdominal pain, nausea, fever, vomiting of fecal infusion due to malposition of tube, discomfort during tube placement, headache, vomiting of bowel preparation after replacement of nasoduodenal tube before FMT start, vomiting, mild constipation, dizziness, malaise, and infectious complications.

Reasons for downgrading:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a dichotomous outcome: small sample size, rare event
4. Imprecise effect estimate for a dichotomous outcome: confidence interval includes both negligible effect and appreciable benefit or harm for treatment group.
5. Imprecise effect estimate for a dichotomous outcome: unknown confidence interval

5.8 Strength of Evidence Summary: Differential Efficacy and Safety Results

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
CDI: Frozen vs. Fresh Feces for FMT									
Differential Efficacy or Safety	13 weeks after the last FMT	1 RCT (Lee)	N= 219	Yes[1, 2] (-2)	Unknown	No	Yes[3] (-1)	Conclusion: No firm conclusions can be made. Insufficient evidence precludes firm conclusions. For the overall population, there were no differences between frozen versus fresh groups in achieving cure within 13 weeks of up to two FMT procedures. None of the subgroups analyzed appeared to modify this outcome based on overlap of the 95% confidence intervals, with the possible exception of hospitalization status at the time of FMT: inpatients who received frozen feces responded similarly to those infused with fresh feces (69% vs. 75% (RD -6% (95% CI -23%, 10%)), while outpatients who received frozen feces were significantly more likely to achieve cure than those who were infused with fresh feces (82% vs. 65% (RD 17% (95% CI 1%, 34%)). **Outcome: Cure (FMT with Frozen vs. Fresh Feces)** **Results from subgroups specified *a priori*:** *Subgroup: Age* • Age <65 (n=54): (82% vs. 63%, RD 19% (95% CI -5%, 42%)) • Age ≥65 (n=165): (73% vs. 73%, RD 0% (95% CI -13%, 14%)) Interaction p-value estimate >0.05.* *Subgroup: Hospitalization status at time of FMT* • Inpatient (n=111): (69% vs. 75%, RD -6% (95% CI -23%, 10%))	⊕◯◯◯ INSUFFICIENT

Outcome	F/U	Studies	N	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion	Quality
								• Outpatient (n=107): (82% vs. 65%, RD 17% (95% CI 1%, 34%)) Interaction p-value estimate >0.05.* *Subgroup: CDI Strain Type* • Non-BI/027 (n=40): (75% vs. 90%, RD -15% (95% CI -38%, 8%) • BI/027 (n=29): (67% vs. 71%, RD -5% (95% CI -38%, 29%)) • Strain type not tested (n=150): (77% vs. 65%, RD 12% (95% CI -3%, 26%)) Interaction p-value estimate >0.05.* **Results from subgroups NOT specified *a priori*:** *Subgroup: Baseline CDI severity* • Mild (n=74): (81% vs. 85%, RD -4% (95% CI -22%, 13%)) • Moderate (n=100): (69% vs. 57%, RD 13% (95% CI -6%, 31%)) • Severe (n=45): (78% vs. 78%, RD 0% (95% CI -25%, 25%)) Interaction p-value estimate >0.05.*	
CDI: All other comparisons									
Differential Efficacy or Safety	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT
IBD									
Differential Efficacy or Safety	Any	0 RCTs						No evidence	⊕◯◯◯ INSUFFICIENT

CDI: *Clostridium difficile* infection; CI: confidence interval; IBD: inflammatory bowel disease; RD: risk difference
*Interaction p-value not reported by the study; estimated to be >0.05 due to substantial overlap in the confidence intervals for the subgroups of interest

Reasons for downgrading:

1. Serious risk of bias: the study violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Serious risk of bias in evaluation of HTE: no formal test for interaction was done; relatively high number of subgroups tested; no hypotheses stated regarding impact of subgroups on cure rate
3. Imprecise effect estimate for a dichotomous outcome: small sample size

5.9 Strength of Evidence Summary: Cost Effectiveness

CDI

Study characteristics

Five cost utility analyses (CUA)[71,75,88,132,133] were included and evaluated the impact of FMT compared with antibiotic(s) in hypothetical patients with CDI. Four[71,75,132,133] of the CUA were relatively well-conducted, with QHES scores ranging from 71 to 89; one of the studies[88] had more methodological limitations, with a QHES score of 54 (Appendix Table E4).

The studies were conducted between 2011 and 2015 in the US[71,132,133], Canada[75], or Australia[88] and the majority were conducted from a payer perspective. The time horizon varied from 90 days to one year. Costs were reported in 2011 to 2015 US, Canadian, or Australian dollars. Cost data were derived from a variety of sources, including CMS in the three studies conducted from a US perspective. The components of cost data included that of the treatment (typically to include donor testing for FMT), hospitalization for recurrent CDI, adverse events, and outpatient visits.

The clinical effectiveness outcome was reported in terms of quality-adjusted life years (QALY), the values for which were derived from published literature (e.g., RCTs, cohort studies, and/or case series). The components used to derive the QALY included cure, recurrence following initial cure, mortality, adverse events, colectomy, fulminant colitis, hospitalization, and ileostomy. In general, assumed cure rates for recurrent CDI following FMT (any route) as reported by the economic analyses were higher (range, 81.3% to 94.5%) than those reported following a single FMT (any route) as reported by studies included in this HTA (RCTs: range, 51.5% to 80%; cohort studies: range, 93% to 96%; case series: range 52% to 94%).

Results

FMT via colonoscopy was found to be dominant[133] or more cost effective[71,75,88] compared to vancomycin in all four studies of patients with recurrent CDI. Conclusions were similar when comparing FMT to metronidazole[71,75] or fidaxomicin[71,75]. For the initial CDI occurrence, one study[132] found that FMT via colonoscopy was dominant over vancomycin alone. In general, sensitivity analyses supported the conclusion that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI.

Conclusions and Limitations

In general, results from the five included CUA suggested that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI. Limitations included lack of long-term follow-up, use of hypothetical populations, use of nonrandomized studies for assumptions regarding clinical outcomes, assumed high cure rates and relatively low recurrence rates following FMT, and no analysis of severe and/or complicated CDI. Overall, the studies were relatively well-conducted.

IBD

No full economic evaluations were conducted on patients with IBD.

References

1. (NIDDK) TNIoDaDaKD. Digestive Diseases Statistics for the United States. Available at: http://www.niddk.nih.gov/health-information/health-statistics/Pages/digestive-diseases-statistics-for-the-united-states.aspx. 2014.
2. Aas J, Gessert CE, Bakken JS. Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. Clin Infect Dis 2003;36:580-5.
3. Administration. UFaD. Guidance for industry: Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat Clostridium difficile infection not responsive to standard therapies. Available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm361379.htm. 2013.
4. Agrawal M, Aroniadis OC, Brandt LJ, et al. The Long-term Efficacy and Safety of Fecal Microbiota Transplant for Recurrent, Severe, and Complicated Clostridium difficile Infection in 146 Elderly Individuals. J Clin Gastroenterol 2015.
5. Allegretti JR, Korzenik JR, Hamilton MJ. Fecal microbiota transplantation via colonoscopy for recurrent C. difficile Infection. J Vis Exp 2014.
6. America CsCFo. Surgery for Crohn's Disease & Ulcerative Colitis. Available at: http://www.ccfa.org/resources/surgery-for-crohns-uc.html. 2010.
7. America CsCFo. The Facts About Inflammatory Bowel Diseases. Available at: http://www.ccfa.org/assets/pdfs/updatedibdfactbook.pdf. 2014.
8. Anderson JL, Edney RJ, Whelan K. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. Alimentary pharmacology & therapeutics 2012;36:503-16.
9. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
10. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults: a systematic review. JAMA 2015;313:398-408.
11. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol 2011;9:1044-9.
12. Bauer MP, Kuijper EJ, van Dissel JT, European Society of Clinical M, Infectious D. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). Clin Microbiol Infect 2009;15:1067-79.
13. Baxter M, Colville A. Adverse events in faecal microbiota transplant: a review of the literature. J Hosp Infect 2016;92:117-27.

14. Berkman ND, Lohr KN, Ansari M, al. e. Chapter 15. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. 2013.
15. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw Index. Inflamm Bowel Dis 2006;12:304-10.
16. Bien J, Palagani V, Bozko P. The intestinal microbiota dysbiosis and Clostridium difficile infection: is there a relationship with inflammatory bowel disease? Therap Adv Gastroenterol 2013;6:53-68.
17. Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. Curr Gastroenterol Rep 2013;15:337.
18. Bowman KA, Broussard EK, Surawicz CM. Fecal microbiota transplantation: current clinical efficacy and future prospects. Clin Exp Gastroenterol 2015;8:285-91.
19. Boye B, Jahnsen J, Mokleby K, et al. The INSPIRE study: are different personality traits related to disease-specific quality of life (IBDQ) in distressed patients with ulcerative colitis and Crohn's disease? Inflamm Bowel Dis 2008;14:680-6.
20. Brandt LJ. American Journal of Gastroenterology Lecture: Intestinal microbiota and the role of fecal microbiota transplant (FMT) in treatment of C. difficile infection. The American journal of gastroenterology 2013;108:177-85.
21. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol 2012;107:1079-87.
22. Poop Banking to Enable Fecal Transplants: Curing Clostridium difficile, the #1 Hospital Acquired Infection in the United States. 2014. (Accessed June 14, 2016, at https://openforum.hbs.org/challenge/hbs-hms-health-acceleration-challenge/refinement/poop-banking-curing-clostridium-difficile-the-1-hospital-acquired-infection-in-the-united-states.)
23. Butler MO, A.; Drekonja, D.; Shaukat, A.; Schwehr, N.; Shippee, N.; Wilt, T.J. Early Diagnosis, Prevention, and Treatment of Clostridium difficile: Update: Agency for Healthcare Research and Quality Effective Health Care Program; 2016.
24. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. J Clin Gastroenterol 2014;48:693-702.
25. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther 2015;41:835-43.
26. Centers for Disease Control and Prevention. Antibiotic/Antimicrobial Resistance: Biggest Threats: Clostridium Difficile. Available at: http://www.cdc.gov/drugresistance/biggest_threats.html 2015.
27. Centers for Disease Control and Prevention. Nearly half a million Americans suffered from Clostridium diccile infections in a single year: Press release. Available at: http://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html. 2015.
28. Chapman JRH, B.P.; Dettori, J.R.; Norvell, D.C. Spine Outcomes Measures and Instruments: Thieme; 2007.
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
30. Cheng AC, Ferguson JK, Richards MJ, et al. Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of Clostridium difficile infection. The Medical journal of Australia 2011;194:353-8.

31. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431-55.
32. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. Journal of Crohn's & colitis 2014;8:1569-81.
33. Costello SP, Conlon MA, Vuaran MS, Roberts-Thomson IC, Andrews JM. Faecal microbiota transplant for recurrent Clostridium difficile infection using long-term frozen stool is effective: clinical efficacy and bacterial viability data. Aliment Pharmacol Ther 2015;42:1011-8.
34. Costello SP, Tucker EC, La Brooy J, Schoeman MN, Andrews JM. Establishing a Fecal Microbiota Transplant Service for the Treatment of Clostridium difficile Infection. Clin Infect Dis 2016;62:908-14.
35. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. Br J Sports Med 2011;45:966-71.
36. Cui B, Feng Q, Wang H, et al. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. J Gastroenterol Hepatol 2015;30:51-8.
37. Daloiso V, Minacori R, Refolo P, et al. Ethical aspects of Fecal Microbiota Transplantation (FMT). Eur Rev Med Pharmacol Sci 2015;19:3173-80.
38. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med 2011;365:1713-25.
39. Danese S, Sans M, Fiocchi C. Inflammatory bowel disease: the role of environmental factors. Autoimmun Rev 2004;3:394-400.
40. Debast SB, Bauer MP, Kuijper EJ, European Society of Clinical M, Infectious D. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect 2014;20 Suppl 2:1-26.
41. Drekonja D, Reich J, Gezahegn S, et al. Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. Ann Intern Med 2015;162:630-8.
42. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery 1958;44:854-9.
43. Eliadou E, Day AS, Thompson-Fawcett MW, et al. New Zealand Society of Gastroenterology Guidelines for the Management of Refractory Ulcerative Colitis. The New Zealand medical journal 2015;128:63-76.
44. Excellence NIfHaC. Faecal microbiota transplant for recurrent Clostridium difficile infection, Interventional procedure guidance2013 18 April 2013.
45. Management of severe ulcerative colitis in adults. 2016. (Accessed May 11, 2016, at http://www.uptodate.com/contents/management-of-severe-ulcerative-colitis-in-adults.)
46. Foerster V. Fecal Microbiota Transplantation (Fecal Transplant) for Adults with Inflammatory Bowel Disease. CADTH Issues in Emergine Health Technologies Informing Decisions About New Health Technologies 2015.
47. Food U, Administration D. Draft guidance for industry: enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat Clostridium difficile infection not responsive to standard therapies. ^ eds Book Draft Guidance for

Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium Difficile Infection Not Responsive to Standard Therapies City: Government Printing Office 2014:10814-5.

48. Frank DN, Pace NR. Gastrointestinal microbiology enters the metagenomics era. Curr Opin Gastroenterol 2008;24:4-10.
49. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A 2007;104:13780-5.
50. Furuya-Kanamori L, Doi SA, Paterson DL, et al. Upper Versus Lower Gastrointestinal Delivery for Transplantation of Fecal Microbiota in Recurrent or Refractory Clostridium difficile Infection: A Collaborative Analysis of Individual Patient Data From 14 Studies. J Clin Gastroenterol 2016.
51. Garborg K, Waagsbo B, Stallemo A, Matre J, Sundoy A. Results of faecal donor instillation therapy for recurrent Clostridium difficile-associated diarrhoea. Scand J Infect Dis 2010;42:857-61.
52. Ghouri YA, Richards DM, Rahimi EF, Krill JT, Jelinek KA, DuPont AW. Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease. Clin Exp Gastroenterol 2014;7:473-87.
53. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis 2011;53:994-1002.
54. Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therap Adv Gastroenterol 2013;6:295-308.
55. Guo B, Harstall C, Nguyen T, Ohinmaa A. Fecal transplantation for the treatment of *Clostridium difficile*-associated diseases or ulcerative colitis: Institute of Health Economics Alberta Canada; 2011.
56. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96:804-10.
57. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.
58. Herpers BLV, B.; Burkhardt, O.; Blom, H.; Biemond-Moeniralam, H.S.; Hornef, M.; Welte, T.; Kuijper, E.J. Intravenous Tigecycline as Adjunctive or Alternative Therapy for Severe Refractory Clostridium difficile Infection. Clinical Infectious Diseases 2009;48:1732-5.
59. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991;12:439-47.
60. Ianiro G, Bibbo S, Scaldaferri F, Gasbarrini A, Cammarota G. Fecal microbiota transplantation in inflammatory bowel disease: beyond the excitement. Medicine (Baltimore) 2014;93:e97.
61. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology 1994;106:287-96.
62. Johns Hopkins Medicine. Fecal transplantation (bacteriotherapy). Available at: http://www.hopkinsmedicine.org/gastroenterology_hepatology/clinical_services/advanced_endoscopy/fecal_transplantation.html.
63. Jorup-Ronstrom C, Hakanson A, Sandell S, et al. Fecal transplant against relapsing Clostridium difficile-associated diarrhea in 32 patients. Scand J Gastroenterol 2012;47:548-52.
64. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol 2007;5:1424-9.

65. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. The American journal of gastroenterology 2013;108:500-8.
66. Keighley MR, Burdon DW, Arabi Y, et al. Randomised controlled trial of vancomycin for pseudomembranous colitis and postoperative diarrhoea. Br Med J 1978;2:1667-9.
67. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol 2014;109:1065-71.
68. Kelly CR, Kahn S, Kashyap P, et al. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. Gastroenterology 2015;149:223-37.
69. Kelly CR, Kunde SS, Khoruts A. Guidance on preparing an investigational new drug application for fecal microbiota transplantation studies. Clin Gastroenterol Hepatol 2014;12:283-8.
70. Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol 2016.
71. Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of competing strategies for management of recurrent Clostridium difficile infection: a decision analysis. Clin Infect Dis 2014;58:1507-14.
72. Kronman MP, Nielson HJ, Adler AL, et al. Fecal microbiota transplantation via nasogastric tube for recurrent clostridium difficile infection in pediatric patients. J Pediatr Gastroenterol Nutr 2015;60:23-6.
73. Kunde S, Pham A, Bonczyk S, et al. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. J Pediatr Gastroenterol Nutr 2013;56:597-601.
74. Lagier JC, Delord M, Million M, et al. Dramatic reduction in Clostridium difficile ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: a preliminary report. Eur J Clin Microbiol Infect Dis 2015;34:1597-601.
75. Lapointe-Shaw L, Tran KL, Coyte PC, et al. Cost-Effectiveness Analysis of Six Strategies to Treat Recurrent Clostridium difficile Infection. PLoS One 2016;11:e0149521.
76. Lashner BA. Crohn's Disease. Available at: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/crohns-disease/. 2013.
77. Lee CH, Belanger JE, Kassam Z, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. Eur J Clin Microbiol Infect Dis 2014;33:1425-8.
78. Lee CH, Steiner T, Petrof EO, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 2016;315:142-9.
79. Li YT, Cai HF, Wang ZH, Xu J, Fang JY. Systematic review with meta-analysis: long-term outcomes of faecal microbiota transplantation for Clostridium difficile infection. Aliment Pharmacol Ther 2016;43:445-57.
80. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011;364:422-31.

81. Lu CL, Liu CY, Liao CH, Huang YT, Wang HP, Hsueh PR. Severe and refractory Clostridium difficile infection successfully treated with tigecycline and metronidazole. Int J Antimicrob Agents 2010;35:311-2.
82. MacConnachie AA, Fox R, Kennedy DR, Seaton RA. Faecal transplant for recurrent Clostridium difficile-associated diarrhoea: a UK case series. QJM 2009;102:781-4.
83. Management of mild to moderate ulcerative colitis in adults. UpToDate, 2016. (Accessed June 14, 2016, at http://www.uptodate.com/contents/management-of-mild-to-moderate-ulcerative-colitis-in-adults.)
84. Marra F, Ng K. Controversies Around Epidemiology, Diagnosis and Treatment of Clostridium difficile Infection. Drugs 2015;75:1095-118.
85. Mattila E, Uusitalo-Seppala R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology 2012;142:490-6.
86. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol 2002;97:1769-75.
87. McFee RB, Abdelsayed GG. Clostridium difficile. Dis Mon 2009;55:439-70.
88. Merlo G, Graves N, Brain D, Connelly L. Economic Evaluation of Fecal Microbiota Transplantation for the Treatment of Recurrent Clostridium Difficile Infection in Australia. J Gastroenterol Hepatol 2016.
89. Moayyedi P, Marshall JK, Yuan Y, Hunt R. Canadian Association of Gastroenterology position statement: fecal microbiota transplant therapy. Can J Gastroenterol Hepatol 2014;28:66-8.
90. Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology 2015;149:102-9 e6.
91. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer 1984;53:2002-7.
92. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571-607.
93. National Health Service. Inflamatory Bowel Disease. Available at: http://www.nhs.uk/conditions/inflammatory-bowel-disease/pages/introduction.aspx. 2015.
94. Nelson RL, Kelsey P, Leeman H, et al. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Cochrane Database Syst Rev 2011:CD004610.
95. Nitzan O, Elias M, Peretz A, Saliba W. Role of antibiotics for treatment of inflammatory bowel disease. World J Gastroenterol 2016;22:1078-87.
96. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.
97. FMT Capsule G3, Clinical Efficacy. (Accessed May 11, 2016, at http://www.openbiome.org/fmtcapsules#clinicalefficacy.)
98. Orenstein R, Dubberke E, Hardi R, et al. Safety and Durability of RBX2660 (Microbiota Suspension) for Recurrent Clostridium difficile Infection: Results of the PUNCH CD Study. Clin Infect Dis 2015.
99. Paramsothy S, Borody TJ, Lin E, et al. Donor Recruitment for Fecal Microbiota Transplantation. Inflammatory bowel diseases 2015;21:1600-6.
100. Patel NC, Griesbach CL, DiBaise JK, Orenstein R. Fecal microbiota transplant for recurrent Clostridium difficile infection: Mayo Clinic in Arizona experience. Mayo Clin Proc 2013;88:799-805.

101. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179-87 e1-3.
102. Petrof EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: 'RePOOPulating' the gut. Microbiome 2013;1:3.
103. Levels of evidence and grades of recommendation. Available at: http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf (Accessed July 23, 2015).
104. Postigo R, Kim JH. Colonoscopic versus nasogastric fecal transplantation for the treatment of Clostridium difficile infection: a review and pooled analysis. Infection 2012;40:643-8.
105. Raeissadat SA, Rayegani SM, Hassanabadi H, Rahimi R, Sedighipour L, Rostami K. Is Platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: one year randomized clinical trial. BMC Sports Sci Med Rehabil 2014;6:12.
106. Raeissadat SA, Sedighipour L, Rayegani SM, Bahrami MH, Bayat M, Rahimi R. Effect of Platelet-Rich Plasma (PRP) versus Autologous Whole Blood on Pain and Function Improvement in Tennis Elbow: A Randomized Clinical Trial. Pain Res Treat 2014;2014:191525.
107. Reed EA, R.; Tubbs, C.; Caterino, J.; Theodoropolous, N.; Mangino, J.; Lustberg, M. Fecal Microbiota Transplant (FMT) for the Treatment of Clostridium difficile Infection: The Ohio State University, Wexner Medical Center; 2014.
108. Relman DV, R.J.; Rustgi, A.K.; Wang, K.K.; Bousvaros, A. Re: Current Consensus Guidance on Donor Screening and Stool Testing for FMT2013.
109. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 2015;149:110-8 e4.
110. Rossen NG, MacDonald JK, de Vries EM, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. World journal of gastroenterology 2015;21:5359-71.
111. Rubin TA, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. Anaerobe 2013;19:22-6.
112. Russell GH, Kaplan JL, Youngster I, et al. Fecal transplant for recurrent Clostridium difficile infection in children with and without inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2014;58:588-92.
113. Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. Appendectomy protects against ulcerative colitis. Gastroenterology 1994;106:1251-3.
114. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462-76.
115. Sachs RE, Edelstein CA. Ensuring the safe and effective FDA regulation of fecal microbiota transplantation. Journal of Law and the Biosciences 2015.
116. Antibiotics for treatment of inflammatory bowel diseases. UpToDate, 2015. (Accessed May 11, 2016, at http://www.uptodate.com/contents/antibiotics-for-treatment-of-inflammatory-bowel-diseases.)
117. Satokari R, Mattila E, Kainulainen V, Arkkila PE. Simple faecal preparation and efficacy of frozen inoculum in faecal microbiota transplantation for recurrent Clostridium difficile infection--an observational cohort study. Aliment Pharmacol Ther 2015;41:46-53.
118. Schechter A, Griffiths C, Gana JC, et al. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. Gut 2015;64:580-8.
119. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625-9.

120. Fee Schedule. 2016. (Accessed June 14, 2016, at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/clinlab.html.)
121. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Medical care 2005;43:203-20.
122. Smith MB, Kelly C, Alm EJ. Policy: How to regulate faecal transplants. Nature 2014;506:290-1.
123. Stroehlein JR. Treatment of Clostridium difficile Infection. Current treatment options in gastroenterology 2004;7:235-9.
124. Surawicz CM. Reining in recurrent Clostridium difficile infection--who's at risk? Gastroenterology 2009;136:1152-4.
125. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 2013;108:478-98; quiz 99.
126. Technology HPACo. Technology Brief Update, Faecal microbiota transplantation: State of Queesnland, Queensland Department of Health; 2014.
127. Teruel C, Garrido E, Mesonero F. Diagnosis and management of functional symptoms in inflammatory bowel disease in remission. World J Gastrointest Pharmacol Ther 2016;7:78-90.
128. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. Am J Sports Med 2011;39:2130-4.
129. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). Inflamm Bowel Dis 2009;15:1218-23.
130. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology 2007;133:423-32.
131. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013;368:407-15.
132. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of treatment strategies for initial Clostridium difficile infection. Clin Microbiol Infect 2014;20:1343-51.
133. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of fecal microbiota transplantation for recurrent Clostridium difficile infection. Infect Control Hosp Epidemiol 2015;36:438-44.
134. Vyas D, Aekka A, Vyas A. Fecal transplant policy and legislation. World journal of gastroenterology 2015;21:6-11.
135. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998;43:29-32.
136. Waye A, Atkins K, Kao D. Cost Averted With Timely Fecal Microbiota Transplantation in the Management of Recurrent Clostridium difficile Infection in Alberta, Canada. J Clin Gastroenterol 2016.
137. Wenisch C, Parschalk B, Hasenhundl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. Clin Infect Dis 1996;22:813-8.
138. West S KV, Carey TS, et. al. Systems to Rate the Strength of Scientific Evidence. Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center, Contract No. 290-97-0011). In: Agency for Healthcare Research and Quality, Rockville, MD; 2002.

139. Wilcox MH. Updated guidance on the management and treatment of Clostridium difficile infection: Public Health England 2013.
140. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980;45:2220-4.
141. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. JAMA 2014;312:1772-8.
142. Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis 2014;58:1515-22.
143. Zallot C, Peyrin-Biroulet L. Deep remission in inflammatory bowel disease: looking beyond symptoms. Curr Gastroenterol Rep 2013;15:315.